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ON CERTAIN VASCULAR EFFECTS OF CURARE IN MAN: THE "HISTAMINE" REACTION[1]

D. GROB, J. L. LILIENTHAL, JR. AND A. M. HARVEY

From the Physiological Division, Department of Medicine, The Johns Hopkins University and Hospital

Curare possesses in high degree the property of blocking the transmission of impulses across synaptic and neuromuscular junctions (8, 9). In recent years curare has been made available in a purified form which permits rigid pharmacological standardisation. As a result, curare has been employed widely for its lissive and paralysing effects to relax skeletal muscle in a variety of clinical applications, including surgical anaesthesia (18), endoscopy (2), convulsive shock therapy (6), convulsive disorders, particularly tetanus (43, 44), and spastic and dystonic states (10, 40).

However, the clinical application of the predominant action of curare on skeletal muscle has brought to light actions on other systems which have introduced certain limitations in the general use of curare. The following side-actions of curare and of its active principle, crystalline *d*-tubocurarine chloride, have been reported; the more serious of these have been infrequent and usually have occurred only after prolonged curarisation.

a) *Cardiovascular*—A transient fall in arterial blood pressure accompanied by a subjective feeling of warmth, giddiness and headache is a frequent occurrence following a single therapeutic dose of 50 to 100 units (13, 14, 25, 43). Occasionally the hypotension has been severe (12) and during prolonged curarisation shock with hemoconcentration has sometimes supervened (34). Similar reactions have been produced in experimental animals (19, 30, 35). The rapidity of administration of curare, as well as the dose, are important factors in the manifestation of its cardiovascular and other pharmacologic effects (19). The drug has been found to have no effect on the electrocardiogram of man (39) or animals (30).

b) *Respiratory*—The development of bronchospasm varying from

[1] Work done under a contract between the Office of Naval Research, U. S. Navy Department, and the Johns Hopkins University.

mild to fatal in degree has been reported in man and in animals (17, 43 to 47, 49).

c) *Secretory*—Excessive salivary and bronchial secretion has been noted following the administration of therapeutic doses to man (13, 14, 47) and in the experimental animal (46).

d) *Central Nervous System*—Smaller doses are frequently associated with slight drowsiness, confusion, or euphoria (20, 25), while large doses may result in depression of electroencephalographic activity (40) and unconsciousness (47). In the frog large doses may cause brain potentials to vanish (16, 36). However, recently a study of a human subject under profound curarisation revealed no alterations in the electroencephalogram, consciousness and sensorium (40a).

e) *Skin*—A few instances of urticaria have been noted following the administration of curare prior to metrazol shock (6).

Several experimental studies have established that the depression of neuromuscular conduction induced by curare may be lightened by eserine and neostigmine (3, 7), acetylcholine and epinephrine (38), potassium (48) and guanidine (24). But recently certain observations in man and animals (26, 34) have indicated that the use of neostigmine as an antidote to large doses of curare or *d*-tubocurarine has failed to prevent death, and that large doses of neostigmine may even increase the toxicity of sublethal doses of curare. Other observations have indicated that the cardiovascular and respiratory effects of curare may be lessened by epinephrine and ephedrine (25, 44, 47, 49), and that ephedrine may increase the antidotal value of small doses of neostigmine (26).

Recently Comroe and Dripps (11) have reported observations on the vascular effects of curare which parallel part of the study to be reported here. They offered the suggestion that these effects were due to the action of histamine and might be prevented by the newer anti-histamine agents.

The experiences of many investigators which have been summarised briefly above, together with the observation that the intra-arterial injection of curare produced extraordinary vascular changes in the injected area (21) indicated the necessity for investigation of the actions of curare other than those on neuromuscular mechanisms. This

communication reports a study of certain vascular effects of curare observed in human subjects.

METHODS

The following drugs were used in this study:

Curare (Intocostrin, Squibb)-containing 20 units per ml. in aqueous solution with 0.5 per cent chlorobutanol as a preservative (pH 4.6). *d-Tubocurarine chloride*[2] (Squibb)—the crystalline active principle of curare in a concentration of 20 units per ml. (containing 2.7 mg. per ml., and equivalent to 20 units or 20 mg. of standard curare) in aqueous solution of 0.5 per cent chlorobutanol (pH 3.5). *Histamine phosphate*—Aqueous solutions containing 2 mg. and 0.125 mg. of histamine base per ml.. *Pyribenzamine*[3] (Ciba)—Aqueous solutions containing 3 mg. and 10 mg. per ml.. *Benadryl*[4] (Parke, Davis)—Aqueous solution containing 30 mg. per ml.. *Beta-erythroidine HCl*[5] (Merck)—Aqueous solutions containing 50 mg. per ml. (pH 6.5) and 100 mg. per ml. (pH 6.0).

Injections of the drugs under study have been made intra-cutaneously, intravenously, intramuscularly and intra-arterially. The latter injections have been made into the brachial artery through an inlying needle introduced through an area of local anesthesia (induced with a 0.5 per cent solution of procaine). Following intra-arterial injection a pneumatic cuff applied above the site of injection was inflated to a pressure of 100 mm. of Hg for two minutes to prolong localisation of the drug. The pneumatic cuff was then deflated slowly over a period of one to two minutes. On several occasions measurements of the volume of the forearm and hand were made by the displacement of water at body temperature in a calibrated cylinder.

In view of speculations regarding the role played by impurities

[2] Kindly furnished by Dr. H. S. Newcomer, E. R. Squibb and Co., New York.

[3] N′-Pyridyl-N′benzyl-N-dimethylethylene diamine hydrochloride, kindly furnished by Ciba Pharmaceutical Products, Inc., Summit, New Jersey.

[4] B-Dimethylaminoethyl benzhydryl ether hydrochloride, kindly furnished by Parke, Davis and Co., Detroit, Michigan.

[5] Kindly furnished by Merck and Co., Inc., Rahway, New Jersey.

present in preparations of curare (45) it may be noted here that in this study the reactions following curare have been indistinguishable, both qualitatively and quantitatively, from those produced by its crystalline active principle, *d*-tubocurarine chloride.

RESULTS

Intracutaneous Administration

The intracutaneous administration of 0.05 ml. of curare or of *d*-tubocurarine solution (containing 1 mg. of curare or 0.135 mg. of crystalline *d*-tubocurarine chloride) into the flexor surface of the forearm of 34 normal subjects resulted in every case in a wheal and flare at the site of the injection with small pseudopodal extensions of the wheal in most cases (Figure 1). The local reaction reached its maximal intensity in five to ten minutes, began to diminish 30 minutes later and disappeared within two to three hours after the injection. The average diameter of the flare at the height of the reaction was 65 mm., of the wheal 20 mm., and the average length of the pseudopodal extensions of the wheal was 9 mm. The subjects reported a transient burning sensation at the site of the injection, sometimes followed by itching.

Intra-arterial Administration

Fifteen to 50 units of curare and of *d*-tubocurarine were administered intra-arterially to 27 normal subjects.

The intra-arterial injection of curare and of *d*-tubocurarine produced identical effects which were proportional to the amount of drug. Immediately following the injection there was a transient burning sensation which extended down the forearm into the hand and fingers. Within one or two minutes after the injection there was marked loss of strength or complete paralysis of all the muscles of the injected forearm and hand. Motor power returned slowly during the next two hours. When the blood pressure cuff was deflated (two minutes after the injection) the injected forearm immediately became intensely hyperemic and engorged and within two minutes after release of the cuff there appeared over the forearm and hand numerous areas of blue and purple discoloration, which did not blanch

on pressure and which resembled ecchymoses (Figure 2). These discolored areas faded gradually and then vanished during the next 30 minutes. As the discoloration diminished the injected forearm and hand gradually swelled with the appearance of a diffuse, firm edema which did not pit on pressure, and with the development of broad

FIG. 1. Right forearm: The response to the intracutaneous injection of 0.05 ml. of curare. Left forearm: The upper wheal represents the site of intracutaneous injection of 0.05 ml. curare after pyribenzamine (see text). The lower wheal is the site of injection of pyribenzamine alone.

wheals over the anterior surface of the forearm. The swelling and wheals were visible 15 minutes after the injection and were maximal 15 minutes later. The wheals were accompanied by a slight sensation of itching. The increase in the volume of the injected forearm and hand varied from 10 to 20 per cent. Where the skin was swollen and

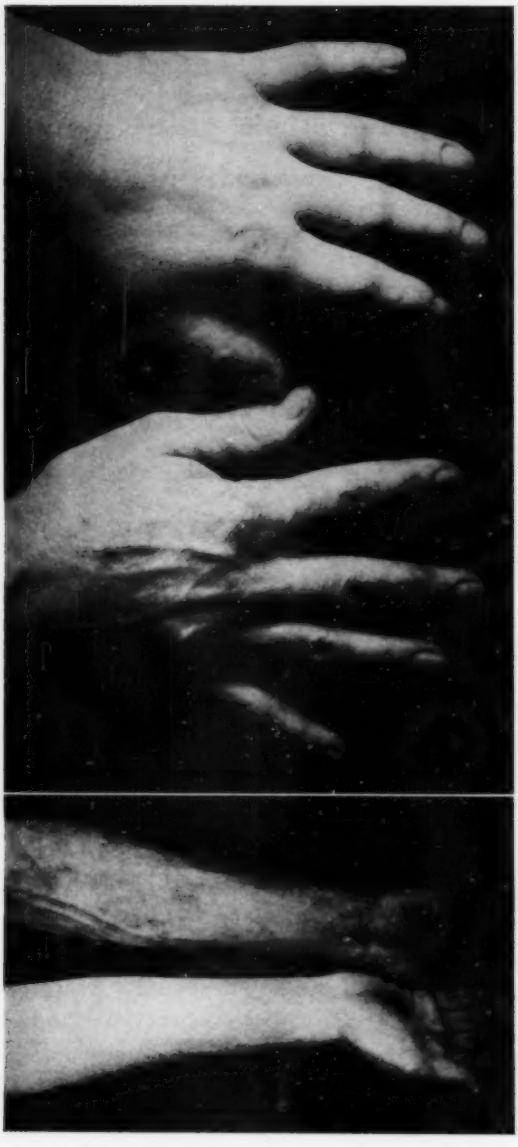

FIG. 2. INJECTION OF 50 UNITS OF *d*-TUBOCURARINE INTO LEFT BRACHIAL ARTERY

Left: five minutes after injection, showing discoloration. Right: 30 minutes after injection, showing edema of hand.

tight, as in the hand, there was some blanching, and in these areas there was also slight hypalgesia to pin prick.

These visible changes were localised to the injected hand and forearm, distal to the point of injection. The wheals gradually diminished and disappeared within a few hours. The swelling persisted for a longer period of time, which was proportional to the amount of drug that had been injected. Following the administration of 30 units of curare or *d*-tubocurarine the swelling was completely gone within 16 hours, and, following 50 units, within 36 hours.

The visible changes in the injected arm were accompanied by evidence of marked vasodilatation, occurring first in the injected forearm and hand and then generally. This was indicated by virtual arterialisation of the venous blood returning from both forearms, as reflected by the blood gas contents (Figure 3). Peripheral vasodilatation was also indicated by the progressive rise in the skin temperature of both upper extremities (measured in a cold room by means of skin thermocouples) from a pre-injection temperature of about 20°C. to a maximum of 32°C. (Figure 4). The skin temperature rose a little more rapidly and to a slightly higher level in the injected arm than in the opposite arm, and the initial vasodilatation was frequently followed by some evidence of transient vasoconstriction (Figures 4 and 6), which may have been compensatory in nature. Further evidence of generalised vasodilatation was furnished by the subjective feeling of warmth, giddiness and frontal headache, which were experienced following release of the blood pressure cuff, and by a transient fall in blood pressure which averaged 20 mm. of mercury systolic and 10 mm. diastolic.

When the curare or *d*-tubocurarine was injected intra-arterially without temporarily obstructing the venous return proximal to the site of injection the neuromuscular and local and general vascular effects of the drug were significantly reduced in degree and in duration. The application of a blood pressure cuff alone for two minutes, without intra-arterial injection of the drug, did not produce any of the effects described above.

Intravenous and Intramuscular Administration

The injection of 15 to 50 units of curare or of *d*-tubocurarine intravenously (at the rate of 25 units a minute) and intramuscularly re-

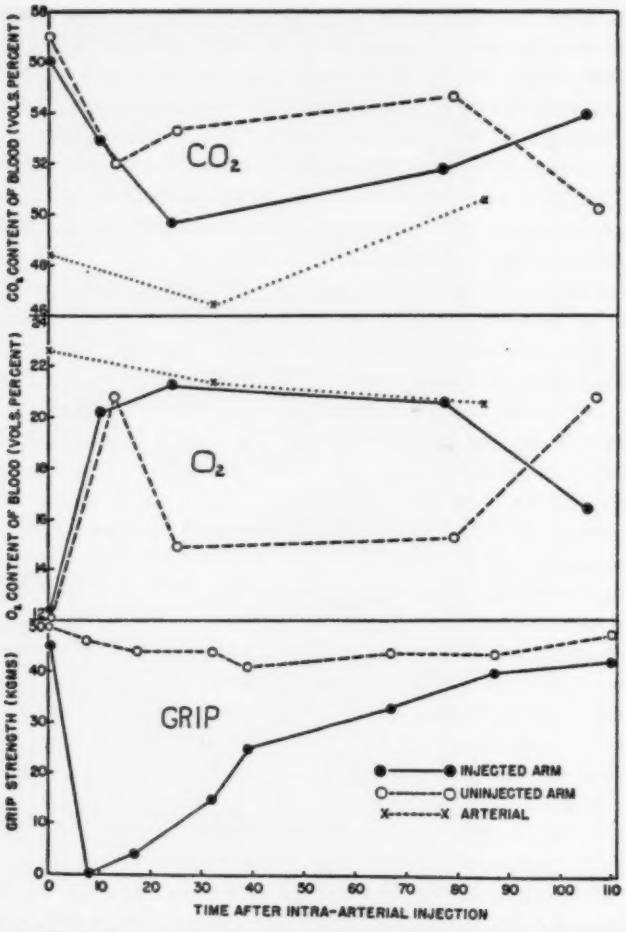

FIG. 3. The influence of the intra-arterial (brachial) administration of 25 units of tubocurarine (3.37 mg.) on the oxygen and carbon dioxide content of the venous blood (Subject W. W.)

●———● Venous blood from the injected arm.
○- - - -○ Venous blood from the opposite arm.
×.....× Arterial blood from the injected arm.

Grip strengths of the hands are recorded below, with the solid line representing the injected arm.

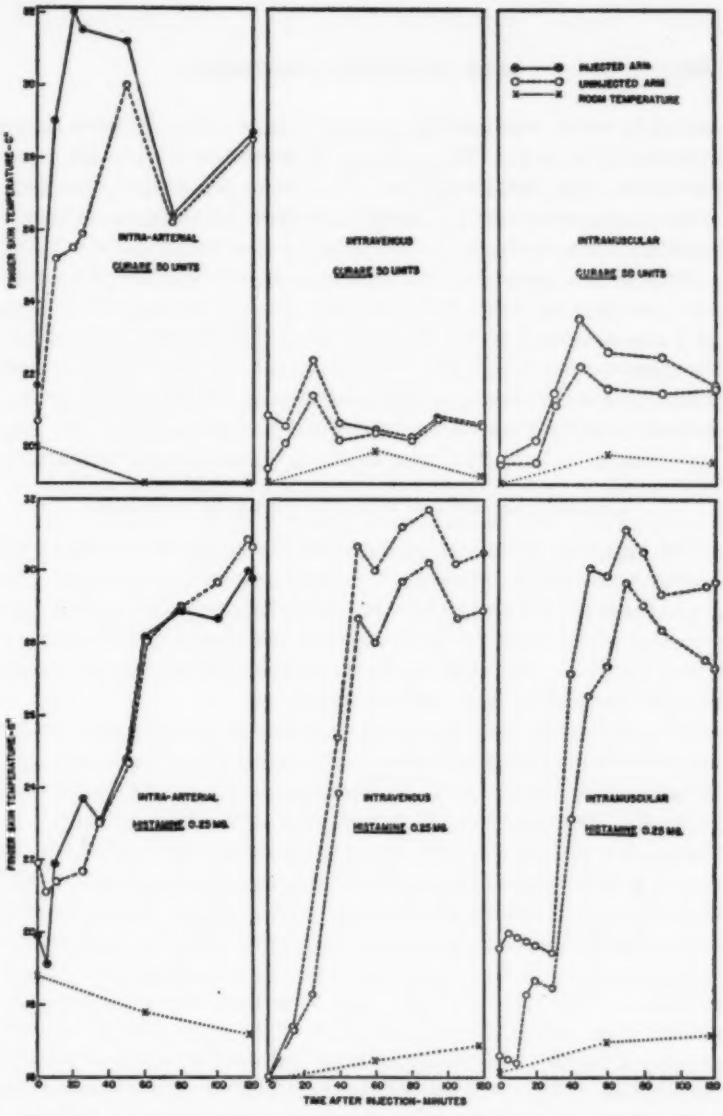

FIG. 4. Comparison between the influence of curare and histamine on finger skin temperature when administered intra-arterially, intravenously, and intramuscularly. (Subject E. T.)

●———● Skin temperature of injected arm.
○- - - -○ Skin temperature of uninjected arm.
×.....× Room temperature

sulted in much less marked vascular effects than did intra-arterial injection (Figure 4). There was no discoloration of the skin, wheal formation, or detectable edema. The rise in skin temperature was a little more pronounced and longer sustained following intramuscular administration of the drug than after its slow intravenous injection.

None of the vascular or neuromuscular effects of curare and *d*-tubocurarine were reproduced by the intra-arterial administration of up to 3 ml. of normal saline or of 0.5 per cent chlorobutanol (pH 4.5), the preservative which was present in the preparations that were used. The intracutaneous administration to 10 normal subjects of 0.05 ml. of 0.5 per cent chlorobutanol did produce a slight flare (average diameter 12 mm., maximum 20 mm.), but no wheal or pseudopods.

Comparison with the Vascular Effects of Histamine

The reported occurrence of hypotension, hemoconcentration, and bronchoconstriction following the administration of curare and *d*-tubocurarine, and the vascular effects of these drugs which have been described above, may be compared with the effects of histamine, an agent which in sufficient concentration produces vasodepression, bronchoconstriction, and capillary damage.

The local wheal and flare and sensation of burning and itching produced by 0.05 ml. of curare or *d*-tubocurarine solution was the same as that produced by 0.05 ml. of histamine solution containing 2 mg. of histamine base per ml. However, the pseudopods produced by histamine were two to three times longer than those produced by curare and *d*-tubocurarine, and the generalised vasodilatation and headache that occasionally followed intracutaneous histamine was never observed after the intracutaneous administration of curare or *d*-tubocurarine. It is of interest that the sensitivity of different subjects to the local effect of curare or *d*-tubocurarine paralleled in general their sensitivity to histamine. One subject with diabetic peripheral neuritis and evidence of partial sympathetic and sensory denervation of his forearms showed no wheal or flare following the intracutaneous injection of histamine in the involved area, and absence of wheal, with a slight flare, following the intracutaneous injection of curare or of chlorobutanol.

The intra-arterial injection of 0.25 mg. of histamine base into the brachial artery produced a transient burning sensation, intense

flushing, transient ecchymotic discoloration, diffuse swelling (41), and slight wheal formation in the injected arm, distal to the point of injection. This was accompanied by evidence of marked vasodilatation, occurring first in the injected arm and then generally, as manifested by a progressive rise in the skin temperature of the upper extremities (Figure 4), by subjective warmth, giddiness, frontal headache, and transient hypotension. The only observed differences between the effects of intra-arterial curare and histamine were the absence of any change in the strength of the injected arm following the administration of histamine, and the somewhat greater systemic effect of the histamine, as manifested by greater subjective warmth, giddiness, headache, and hypotension.

The main difference between the general vascular effects of histamine and of curare was in the greater effectiveness of the intravenous and intramuscular administration of histamine as compared to curare. The administration of curare by these routes produced a much smaller rise in the skin temperature of the upper extremities than did the intra-arterial administration. In contrast, the effect of histamine was approximately the same by any of these routes (Figure 4) (5).

Because of the general similarity between the vascular effects of curare or *d*-tubocurarine, and of histamine, a study was made of the effect of these drugs, administered by various routes, on the secretion of acid by the stomach. The administration of 0.25 mg. of histamine produced approximately the same increase in the secretion of gastric acid, whether injected intra-arterially, intravenously or intramuscularly. On the other hand, while *d*-tubocurarine produced a marked increase in the secretion of gastric acid when administered intra-arterially, it caused only a moderate increase following intramuscular administration, and very little following intravenous administration (Figure 5).

Inhibition of the Vascular Effects of Curare and d-Tubocurarine by Antihistamine Drugs

Pyribenzamine and benadryl, which have been shown to be potent inhibitors of most of the pharmacological effects of histamine (29, 50), were administered in an attempt to block the vascular response to curare.

The intracutaneous administration of 0.05 ml. of pyribenzamine

(3 mg. per ml.), prior to the injection of 0.05 ml. of curare or *d*-tubocurarine (20 units per ml.) into the same site, inhibited the wheal and most of the flare produced by the latter preparations (Figure 1). A similar inhibition was produced by benadryl, but a higher concentration (30 mg. per ml.) was required. The inhibitory effect of pyribenzamine and benadryl also could be demonstrated by mixing these drugs with the curare or *d*-tubocurarine prior to the injection. These amounts of pyribenzamine and benadryl injected intracutane-

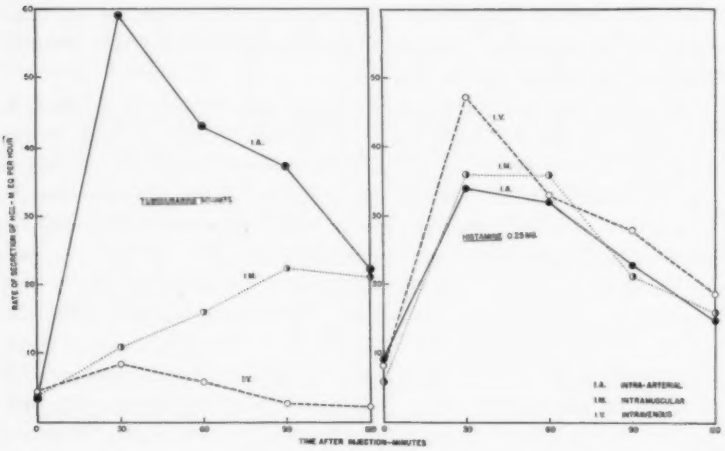

FIG. 5. Comparison between the influence of tubocurarine and histamine on the secretion of gastric acid when administered intra-arterially (●————●), intravenously (○- - - -○), and intramuscularly (◑.....◑). Subject A. G.)

ously had a moderate but less completely inhibitory effect on the wheal and flare produced by 0.1 mg. of histamine base. The oral administration of pyribenzamine or benadryl (200 mg. 100 minutes and again 30 minutes before injection) had a much less markedly inhibitory effect on the wheal and flare produced by intracutaneous curare or histamine than did the local administration. However, measurements demonstrated a reduction in the size of the wheal, flare, and pseudopods produced by each drug, by as much as 40 per cent, and a more rapid disappearance of these local effects.

Pyribenzamine exhibited a markedly inhibitory action on the vascular effects of intra-arterial curare. The intra-arterial injection of 10 mg. of pyribenzamine produced intense pain and a transient, dark red flush in the injected arm. Fifty units of curare were then injected intra-arterially, and the proximal blood pressure cuff released two minutes later. The resulting weakness in the injected arm followed the usual time course (Figure 7) indicating that the injection had been complete. However, the hyperemia, venous engorgement, and ecchymotic discoloration that followed were considerably diminished and there were no wheals and almost no swelling of the injected arm and hand (Figure 6). Likewise, the usual increase in the skin temperature was almost completely inhibited in the injected arm and moderately inhibited in the opposite arm (Figure 7). The same results were obtained by mixing pyribenzamine with curare, in the amounts indicated above, prior to intra-arterial administration. A control injection of 10 mg. of pyribenzamine alone into the brachial artery had no significant effect on the strength or temperature of the extremities (Figure 8).

A similar inhibition of the local swelling, and local and general skin temperature changes produced by the intra-arterial administration of curare occurred following the oral administration of 200 mg. of pyribenzamine 100 and 30 minutes before the injection of 50 units of curare (Figure 7). The oral administration of pyribenzamine alone had no significant effect on the strength or temperature of the extremities (Figure 8).

Absence of Influence of Atropine and Neostigmine on the Vascular Effects of Curare

The wheal and flare produced by the intracutaneous administration of 0.05 ml. of curare (or *d*-tubocurarine) containing 20 units per ml. was not inhibited by the prior injection of 0.05 ml. of atropine sulfate (1.2 mg. per ml.) or neostigmine methylsulfate (0.5 mg. per ml.) into the same site.

Likewise the discoloration, swelling, and wheal formation of the injected arm, and the evidence of peripheral vasodilatation that followed the intra-arterial administration of 50 units of curare were unaffected by the prior intra-arterial administration of 1.2 mg. of atropine

FIG. 6. INJECTION OF 10 MG. PYRIBENZAMINE FOLLOWED BY 50 UNITS OF CURARE INTO THE LEFT BRACHIAL ARTERY.
Compare with Fig. 2

sulfate or 1.5 mg. of neostigmine methylsulfate (Figure 8). The neostigmine did inhibit to some degree the muscular weakness caused by the curare (Figure 8). Identical results were obtained by mixing atropine or neostigmine with curare before intra-arterial administra-

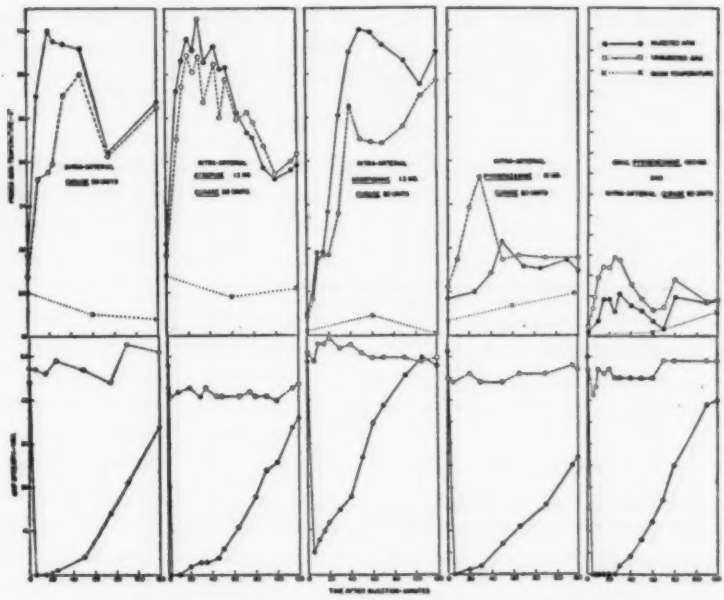

FIG. 7. The influence of 50 units of curare (50 mg.) administered intra-arterially on finger skin temperature and grip strength, and the effect of previously administered atropine (1.2 mg.), neostigmine (1.5 mg.), and pyribenzamine (10 mg.) administered intra-arterially, and pyribenzamine (200 mg. 100 and 30 minutes before injection) administered orally. (Subject E. T.)

●———● Injected arm.
O- - - -O Uninjected arm.
×.....× Room temperature.

tion. The intra-arterial administration of 1.2 mg. of atropine alone had no significant effect on the strength or temperature of the upper extremities (Figure 8) while the intra-arterial injection of 1.5 mg. of neostigmine alone caused immediate weakness, marked sweating,

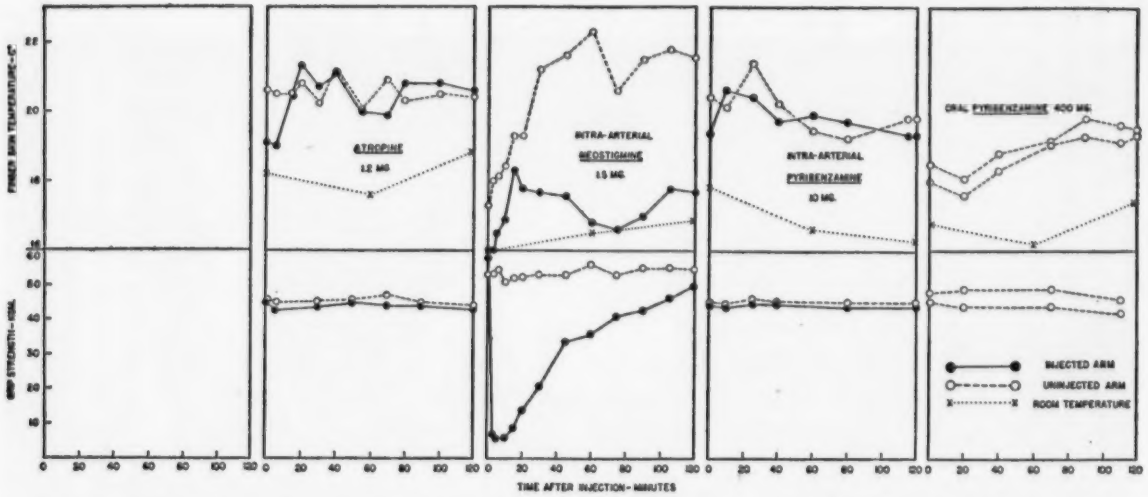

FIG. 8. (Control to Figure 7). The effect of the intra-arterial administration of atropine (1.2 mg.), neostigmine (1.5 mg.) and pyribenzamine (10 mg.), and the oral administration of pyribenzamine (200 mg. 100 and 30 minutes before), on finger skin temperature and grip strength. (Subject E. T.).

●———● Injected arm.
○- - - -○ Uninjected arm.
×.....× Room temperature.

and fasciculations in the injected arm. This was accompanied by a moderate increase in the skin temperature of the upper extremities (Figure 8), and a moderate increase in the oxygen content and decrease in carbon dioxide content of the venous blood of the upper extremities. This evidence of peripheral vasodilatation was less marked in the injected arm than in the opposite arm, perhaps due in part to the cooling effect of the marked sweating of the injected arm.

The Vascular and Central Nervous System Effects of Beta-Erythroidine

Beta-erythroidine is a tertiary ammonium base which, while structurally dissimilar to *d*-tubocurarine, has a similar effect on neuromuscular function (42) and has been used by a few investigators to promote muscular relaxation in shock therapy (12), tetanus (15), and spastic and dystonic states (10). The intravenous administration of a therapeutic dose of beta-erythroidine (300 mg., which is equivalent in neuromuscular effect to about 50 units of curare) has been reported to cause a transient fall in blood pressure (15, 37), rarely shock (12), and occasionally central nervous system symptoms, including drowsiness, confusion, and disorientation (25).

Study of the effects of beta-erythroidine hydrochloride administered intracutaneously to 10 subjects (5 mg. in 0.1 ml. at pH 6.5) and intra-arterially to three subjects (300 mg. in 3 ml. at pH 6.0) revealed vascular and neuromuscular changes similar to those described for curare (and *d*-tubocurarine), except that the degree of swelling, wheal formation, and evidence of local and general vasodilatation that followed intra-arterial administration were less than half as great as that observed after curare or tubocurarine (50 units). The central nervous system effects of beta-erythroidine, however, were much more marked than those mild symptoms which followed the intravenous administration of 60 units of curare.

The intra-arterial or intravenous administration of 150 to 300 mg. (average 200 mg.) of beta-erythroidine to eight normal subjects at the rate of 150 mg. a minute resulted in drowsiness and apprehension in all of the subjects, colored vision (yellow and brown) in three, disorientation, confusion, impairment of memory, and feelings of unreality in two; and uncontrolled crying, exaggerated tremor, and intermittent stammering and aphasia in one. These symptoms persisted

for as long as four hours, and were accompanied by electroencephalographic changes of varying degree in five of the six subjects who were so studied. These consisted of the intermittent appearance of bursts of slow waves (3 to 6 per second) of elevated voltage in all five, usually most marked in the frontal leads and increased by hyperventilation, increase in the potential and frequency of the electrical pattern in four subjects, and increased irregularity in three. In general, the electroencephalographic changes paralleled the severity of the central nervous system symptoms. The intravenous administration of atropine sulfate (1.2 mg.) or neostigmine methylsulfate (1.5 mg.) had no effect on the central nervous system symptoms or electroencephalographic changes.

DISCUSSION

The most prominent and best known pharmacologic action of curare is its ability to relax and paralyse skeletal muscle by inhibiting the transmission of impulses across the neuromuscular junction (8). Other less prominent pharmacologic effects of curare include its ability to produce hypotension, bronchoconstriction, excessive salivation and bronchosecretion, and, in overdose, hemoconcentration, shock, and depression of the central nervous system. Since these effects are produced by crystalline *d*-tubocurarine, as well as by the more commonly used preparations of curare, they appear to be pharmacologic effects of the drug itself and not due to the presence of impurities.

The vascular effects of curare were not inhibited by atropine, which prevents the muscarinic effects of acetylcholine. The swelling and wheal formation that occurred after intra-arterial curare could not be duplicated by the intra-arterial injection of atropine or neostigmine, nor have such effects been observed after intra-arterial acetylcholine (22) or adrenaline (23, 33). These observations, and the absence of significant anticholinesterase activity of *d*-tubocurarine (31) make it seem unlikely that the vascular effects of curare are cholinergic or adrenergic in origin. *d*-Tubocurarine has been reported to increase the rate of loss of potassium ions from isolated muscle (32), but Pearlstein and Weinglass (35) could detect no change in the serum potassium of dogs dying after prolonged curarisation. Preliminary observations of the effects of the intra-arterial administration of potassium chloride revealed that this compound produces severe local pain, but no

swelling or wheals comparable to that produced by curare or histamine (28).

Histamine produced local and systemic vascular effects (as well as increased secretion of gastric acid) which closely resembled the effects of intra-arterial curare. These findings suggest that the intra-arterial administration of curare may cause the release of a histamine-like substance which produces local edema and wheal formation, local and then general vasodilatation, and increased secretion of gastric acid. This substance apparently also may be released following the administration of curare intracutaneously, and to a lesser degree following intravenous and intramuscular injection.

The differences in degrees of histamine-like effects which followed the administration of curare by various routes suggest that the release of a histamine-like substance depends upon the attainment of a critical concentration of curare in certain tissues. An example of this indirect phenomenon is found in the report of West (46) who noted that the parenteral injection of curarine into intact guinea pigs produced bronchoconstriction, while contraction in the isolated bronchus occurred only after prolonged exposure to much higher concentrations of curarine.

Further evidence that the vascular effects of curare may be mediated by a histamine-like substance is provided by the inhibition of the vascular effects, both locally and systemically, by the antihistamine drug, pyribenzamine. Finally, Alam and his coworkers (4) have provided evidence for the release from skeletal muscle of histamine-like substances following the administration of curare. These observers reported that the injection of curare into an artery supplying the limb muscles of dogs caused the liberation into the circulation of a detectable amount of a substance which behaved chemically and biologically like histamine, and which was inactivated by histaminase. This substance was also released after the rapid intravenous administration of curare, and was accompanied by a measurable decrease in the existing store of histamine-like substances in the skeletal muscles, which they believed to be the chief source of the substance liberated into the circulation. This phenomenon was also observed after denervation, and therefore was not thought to be dependent on the paralysing action of curare.

The mechanism for the release of a histamine-like substance after

the administration of curare and of beta-erythroidine remains unknown. Neither *d*-tubocurarine nor beta-erythroidine contains a moiety chemically related to histamine which might serve as a possible source. Histamine-like substances have been extracted from all tissues (1) and their release has been postulated in many other situations, such as allergy, anaphylaxis, and peptone shock, but the mechanism of release has not been elucidated. The wide range of chemical and physical agents that are capable of causing a local wheal and flare (27) emphasises further that the release of histamine-like substances may be a very general phenomenon.

The clinical significance of these observations lies in the reported occurrence during curarisation, especially if prolonged, of vascular and other phenomena which resemble the effects of histamine. The inhibition of such effects by the antihistamine drug, pyribenzamine, without affecting the neuromuscular action of curare, suggests that pyribenzamine may prove to be of value in the prevention and treatment of these histamine-like actions of curare. It is of interest that the vascular effects of curare were not inhibited by neostigmine; in fact, neostigmine itself produced evidence of local and general vasodilatation, which might potentiate the vascular effects of curare. This finding is of clinical significance, since, although neostigmine is capable of counteracting the neuromuscular effects of curare, it has been found to be ineffective or even harmful when used as an antidote to large doses of curare.

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SUMMARY

1. Intracutaneous administration of curare and of *d*-tubocurarine chloride to human subjects produced a local flare and wheal with pseudopods. Intra-arterial administration produced weakness, discoloration, swelling, and wheals of the injected forearm and hand, evidence of local and general vasodilatation, and increased secretion

of gastric acid. Intravenous and intramuscular administration produced no evident swelling or wheals, and less peripheral vasodilatation and secretion of gastric acid.

2. The vascular effects of curare were not inhibited by the prior or simultaneous administration of atropine or of neostigmine.

3. The intracutaneous and intra-arterial administration of histamine produced vascular effects very similar to those of curare. The main difference between the vascular effects of histamine and of curare was in the greater effectiveness of the intravenous and intramuscular administration of histamine in the production of peripheral vasodilatation and increased secretion of gastric acid.

4. The local and general vascular effects of curare were inhibited by the prior or simultaneous administration of the antihistamine drug, pyribenzamine.

5. Beta-erythroidine, a depressant of neuromuscular conduction chemically dissimilar to curare, produced similar but less marked vascular effects. It also produced, in contrast to equivalent doses of curare, moderate central nervous system symptoms and electroencephalographic changes.

6. The vascular effects of curare suggest that the intra-arterial administration of this drug causes the release of a histamine-like substance which acts first locally, and then systemically. This substance apparently also is released after intracutaneous administration, and to a lesser degree after intramuscular and slow intravenous injection.

7. The release of a histamine-like substance following the administration of curare may explain the reported occurrence during curarisation of vascular and other phenomena which resemble the effects of histamine. Pyribenzamine may prove to be of value in the prevention and treatment of these histamine-like actions of curare.

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PHYSIOLOGICAL STUDIES IN CONGENITAL HEART DISEASE*

III. Results Obtained in Five Cases of Eisenmenger's Complex

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The two previous reports in this series have dealt with physiological methods employed in the study of congenital heart disease and the results obtained from these methods in patients with tetralogy of Fallot (1, 2). This paper presents the physiological studies in 5 selected cases of congenital heart disease which had been clinically classified in the group commonly designated as Eisenmenger's complex. They were chosen out of a total of 8 similar cases since they represented most clearly the physiological and clinical aspects of this disease. The clinical findings in these cases will be discussed mainly in their relationship to the physiological data obtained.

In Eisenmenger's original publication the complex which bears his name consisted of a high ventricular septal defect, an aorta which overrode both the right and left ventricles (dextroposition of the aorta), and a dilated pulmonary artery (3). According to current concepts, the outstanding clinical features are cyanosis, which usually develops later in life, clubbing of the fingers, and in many patients the occurrence of hemoptyses (4). A loud systolic murmur is usually heard over the base of the heart to the left of the sternum. On fluoroscopy Eisenmenger's complex is characterized by a prominent pulmonary conus and marked vascular shadows with expansile pulsations in the lung fields (5).

The physiological methods used in this report have been described in detail in the first paper of this series (1). For reasons of clarity, formulae used for the determination of various volume flows by means of the Fick principle are restated and redefined at this time.

1. Pulmonary Capillary Blood Flow represents the total amount of blood flowing through the lungs.

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Pulmonary capillary flow ml. per min.

$$= \frac{\text{CO}_2 \text{ output ml. per min.}}{\text{CO}_2 \text{ content of blood reaching alveoli (vol. per cent)} - \text{CO}_2 \text{ content of pulmonary vein blood (vol. per cent)}} \times 100$$

Normally, pulmonary capillary flow equals pulmonary artery flow (6). In the presence of collateral circulation pulmonary capillary flow exceeds pulmonary artery flow.

2. Pulmonary Artery Flow is the blood flowing through the pulmonic valve into the pulmonary artery.

Pulmonary artery flow (ml. per min.)

$$= \frac{\text{O}_2 \text{ intake (ml. per min.)}}{\text{O}_2 \text{ content of pulmonary vein blood (vol. per cent)} - \text{O}_2 \text{ content of pulmonary artery blood (vol. per cent)}} \times 100$$

The average normal pulmonary artery flow is approximately 3000 cc./min./M^2 (7).

3. Oxygen content of pulmonary vein (vol. per cent) = percentage O_2 saturation of pulmonary vein $\times$ O_2 capacity (vol. per cent). The percentage of oxygen saturation of the pulmonary vein was assumed to be 95 per cent.

4. Collateral Circulation to the Lung represents the volume flow of blood to the lung through channels other than the pulmonary artery. Collateral circulation to the lung (ml. per min.) = pulmonary capillary flow (ml. per min.) − pulmonary artery flow (ml. per min.)

5. Systemic Blood Flow is the volume of blood perfusing the systemic blood vessels.

Systemic blood flow (ml. per min.)

$$= \frac{\text{O}_2 \text{ intake (ml. per min.)}}{\text{O}_2 \text{ content of peripheral arterial blood (vol. per cent)} - \text{O}_2 \text{ content of right auricular blood (vol. per cent)}} \times 100$$

The systemic blood flow in the normal individual equals pulmonary artery flow.

6. The Intracardiac Shunt is the rate of blood flow from one ventricle to the other through a septal defect or from one ventricle into

the overriding aorta. According to its overall direction, the shunt is referred to as being from right to left or from left to right.

Intracardiac shunt right to left (ml. per min.) = volume of blood flow through the systemic circulation (ml. per min.) − volume of blood flow through the pulmonary artery (ml. per min.)

Intracardiac shunt left to right (ml. per min.) = volume of blood flow through pulmonary artery (ml. per min.) − volume of blood flow through the systemic circulation (ml. per min.)

7. The Effective Pulmonary Blood Flow is the amount of mixed venous blood which, having returned to the heart from the systemic circulation, eventually reaches the pulmonary capillaries.

$$\text{Effective pulmonary blood flow (ml. per min.)} = \frac{O_2 \text{ intake (ml. per min.)}}{O_2 \text{ content of pulmonary vein blood (vol. per cent)} - O_2 \text{ content of right auricular blood (vol. per cent)}} \times 100$$

Normally the effective pulmonary blood flow equals pulmonary artery flow.

The assumptions made in these calculations have been discussed in detail in a previous communication. Special emphasis was placed on the difficulty in deriving the oxygen saturation of pulmonary vein blood, which was assumed to be 95 per cent. The validity of this figure has been confirmed in cases with pulmonic stenosis by analyses of blood obtained directly from the pulmonary vein (2). In patients with Eisenmenger's complex, sampling of pulmonary vein blood has been impossible. Furthermore, the question has been raised as to whether the cyanosis in Eisenmenger's complex might be the result of difficulties in the transfer of oxygen across the pulmonary alveolar membrane (8). These considerations cast some doubt on the validity of formula # 2 and 7 since it is based on the assumption that the saturation of the pulmonary vein blood is 95 per cent. If the actual saturation of pulmonary vein blood were below this value, figures obtained for pulmonary artery flow as calculated in this paper from equation 2 would be too low. The agreement between the pulmonary capillary flow and pulmonary artery flow, indicates that the calculated figures obtained for pulmonary artery flow may be accurate. Pulmonary

diffusion factors constitute a much smaller source of error in the determination of pulmonary capillary flow since the latter entails the use of carbon dioxide. The diffusion coefficient of this gas is so much greater than that of oxygen that pulmonary capillary flow should be accurate even in the presence of alveolar lesions which might develop as a sequence to vascular changes. In 2 cases, in which the elevation of pulmonary arterial pressures indicated increased resistance in the pulmonary bed, the pulmonary capillary flow equaled pulmonary artery flow. Consequently, despite increased pulmonary resistance, the values obtained with oxygen correspond to those obtained with carbon dioxide. This indicates that the use of formula 2 for the determination of pulmonary artery flow is justified in the cases reported in this paper.

Another argument against full saturation of pulmonary vein blood as implied by formula 2 has been the assumption that the intracardiac shunt was predominantly directed toward the right (8). In this case the unsaturation of peripheral arterial blood must be entirely due to pulmonary factors. This assumption was based on the belief that, in the absence of increased pulmonary resistance, the pressure in the aorta must be considerably higher than that in the pulmonary artery. Results to be described in this paper, however, show an increase in systolic and diastolic pressure in the pulmonary artery. This observation indicates increased resistance in the pulmonary vascular bed. It is probable, therefore, that mixing currents from right to left rather than unsaturation of pulmonary vein blood play the predominant role in the production of arterial unsaturation.

CASE STUDIES

Case 1. J. S. (age 10, date of study April 4, 1946). This child was apparently normal at birth. Cyanosis appeared at the age of 2 after an attack of whooping cough. Since that time moderate cyanosis had been evident on exertion. At the time of study she could walk a distance of from 3 to 4 city blocks. Her dyspnea was relieved by squatting. There was no history of hemoptysis.

On physical examination her mucous membranes were found to be slightly cyanotic. There was moderate clubbing of fingers and toes. The blood pressure was 100/70 mm. Hg in the arm. The lungs were normal to percussion and auscultation. On percussion the heart was not enlarged. On auscultation the second pulmonic sound was abnormally loud. A very soft systolic murmur could be heard along the left sternal border. There was no diastolic murmur. On

fluoroscopy the heart was of normal size. In the left anterior oblique position the pulmonary window was not well defined, and in the anteroposterior view the pulmonary conus was prominent. There were marked expansile pulsations in the lung fields. The electrocardiogram showed right axis deviation. Laboratory data revealed a hematocrit of 44 per cent, a hemoglobin of 17 gms. per 100 cc. (Sahli) and a red cell count of 4.7 millions per mm^3.

Physiological studies: The standard exercise test was not performed by this patient. Table II shows that the pulmonary capillary flow was above normal limits and exceeded the pulmonary artery flow, demonstrating the presence of some collateral circulation to the lung. The significant data obtained from catheterization of the heart are illustrated in Table III and may be summarized as follows: (1) The volume flow through the pulmonary artery slightly exceeded the flow through the systemic blood vessels. (2) The oxygen content of the pulmonary artery blood exceeded that of right auricular blood by 3.4 vol. per cent. (3) The effective pulmonary blood flow was 50 per cent below the blood flow through the pulmonary arteries and the oxygen saturation in peripheral arterial blood was 83 per cent. Intracardiac pressures were not recorded.

Comment. The pulmonary artery flow exceeds the systemic flow by only 210 cc. per minute/M^2 (Table III). This is not considered significant evidence for a preponderant left to right shunt. Shunting currents from left to right must exist. This is indicated by the observations that the oxygen content of pulmonary artery blood exceeds that of right auricular blood by 3.4 vol. per cent and that the effective pulmonary blood flow is 50 per cent below the pulmonary artery flow. On the other hand, the presence of concomitant right to left currents is indicated by the finding that the oxygen saturation in peripheral arterial blood is reduced to 83 per cent.

Case 2. J. P. (male, aged 39. Studies begun on July 17, 1946). The patient was told that he was blue at birth. At school his activities were only slightly restricted, but with more strenuous exercise he noticed that he became more short of breath than his playmates. At 12 years of age cyanosis was noticed by the patient for the first time. He had worked for the last 17 years in occupations requiring no undue physical strain. He had had an unusual number of coughs and upper respiratory tract infections during the winter months, and in 1933 he brought up some bright red blood in one of his coughing episodes. At the age of 26 he was

told by his physician that he had congenital heart disease. Since then he has had difficulty in breathing on climbing two or three flights of stairs and had felt that the intensity of cyanosis had progressed. For the last two years he has had a dull ache in the region of the left anterior chest wall. This pain was most frequently noticed in the morning upon arising. Inhalations of oxygen and bed rest have not relieved this distress.

On physical examination there was mild cyanosis of the lips and nail beds. There was no clubbing of the fingers. The lungs were clear to percussion and auscultation. No thrill could be felt over the precordium. The area of cardiac dullness measured 11 cm. to the left in the fifth interspace and 6 cm. to the left in the second intercostal space. The heart rate was 55 beats per minute, and the rhythm was regular. The second pulmonic sound was loud and exceeded the second aortic sound in intensity. A harsh but only moderately loud systolic

TABLE I

Results Obtained from the Standard Exercise Test

NO.	DATE	NAME	SEX	AGE	VENT. LIT. MIN. M^2	CO_2 CC. PER M^2	CO_2 CC. PER L.V.	O_2 CC. PER M^2	O_2 CC. PER L.V.	R.Q.	ARTERIAL BLOOD				NO.
											O_2 Vol. %	CO_2 Vol. %	Cap. Vol. %	Sat. %	
2	7/17/46	J. P.	M	39	Rest 5.22	118	22.6	120	22.7	0.95	23.1	37.3	26.7	87	2
					Exer. 7.40	152	21.6	204	27.6	0.72	15.6	39.2	26.7	61	
3	11/15/46	E. S.	F	19	Rest 4.5	123	27.4	112	25.0	1.10	18.5	36.6	24.2	77	3
					Exer. 6.8	158	23.3	218	32.2	0.72	13.4	40.0	24.2	55	
4	12/11/46	V. S.	F	25	Rest 4.9	94	19.0	104	21.0	0.89	17.0	34.2	20.0	84	4
					Exer. 8.8	202	23.0	229	26.0	0.87					
5	3/12/47	B. S.	M	9	Rest 6.5	142	22.0	158	24.2	0.88	20.1	34.7	24.4	82	5
					Exer. 10.2	221	22.0	241	23.5	0.90					

murmur was heard over the fifth intercostal space half way between the point of maximum impulse and the midsternal line. A diastolic murmur was not audible. Blood pressure in the arm (by ausculation) was 125/75 mm. Hg. The hemoglobin was 19 gms. per 100 cc. of blood (Sahli). The red cell count was 7 millions per cmm. and the hematocrit was 61 per cent. The arm to tongue circulation (decholin) was 40 seconds (single end point). The electrocardiogram revealed left axis deviation in the standard leads.

The fluoroscopic examination showed a large pulmonary artery. There were increased vascular markings and slight pulsations in the lung fields. In the oblique views the heart did not appear enlarged.

Physiological studies: The results of the standard exercise test are summarized in Table I. It can be seen that the oxygen consumed per

liter of ventilation increased. The oxygen saturation of peripheral arterial blood drawn immediately after the exercise was lower than the resting value.

Figures obtained for the determination of pulmonary capillary blood flow are illustrated in Table II. It can be seen that the pulmonary capillary flow was at the lower limit of normal and closely approached the volume flow through the pulmonary artery. The results obtained from right heart catheterization and intubation of the pulmonary artery are shown in Table III. They may be summarized as follows: (1) The pulmonary artery flow slightly exceeded the systemic flow. (2) The blood oxygen content in the pulmonary artery was 2.7 per cent higher than that of right auricular blood. (3) The mean pressure

TABLE II

Data Obtained from Equilibration Method for Determination of Pulmonary Capillary Flow

No.	DATE	NAME	SEX	AGE	SURF. AREA M^2	cc. CO_2 PROD.	R.Q.	MIN. VOL. L/M	CO_2 INCOMING BLOOD			CO_2 OUTGOING BLOOD			PULM. CAP. FLOW L/M/M^2	PULM. ARTERY FLOW L/M/M^2 (CATHETER)	COLLAT. PULM. FLOW L/M/M^2	NO.
									%	mm. Hg	Vol. %	%	mm. Hg	Vol. %				
1	4/ 4/46	J. S.	F	10	1.0	106 calc.	1.3	8.3	4.53	32.0	37.5	3.96	28.0	35.1	4.25	3.65	0.60	1
2	7/18/46	J. P.	M	36	1.7	169	1.0	8.8	4.14	29.5	39.5	3.13	22.4	35.5	2.36	2.48	0	2
3	11/13/46	E. S.	F	19	1.5	163	0.9	6.9	4.70	33.7	41.8	3.8	27.6	38.4	3.11	2.20	0.91	3
4	12/ 9/46	V. S.	F	25	1.5	143	0.9	7.6	3.98	28.6	38.5	3.25	23.3	35.5	3.11	2.71	0.40	4
5	3/13/47	B. S.	M	9	0.9	99	0.7	5.2	4.40	31.8	35.3	3.1	22.4	30.5	2.23	2.28	0	5

in the pulmonary artery recorded with a saline manometer was 65 mm. Hg (Table IV). The effective pulmonary blood flow was approximately 1000 cc. less than the blood flow through the pulmonary artery and the oxygen saturation in the peripheral arterial blood was 84 per cent (Table III).

Comments. The rise in the oxygen consumed per liter of ventilation from rest to exercise demonstrates that the effective blood flow through the lung can increase sufficiently to satisfy the respiratory demands of exercise. It seems significant that the oxygen saturation of peripheral arterial blood which was drawn immediately after the performance of the exercise test is lower than the resting oxygen saturation. This is probably the result of shunting of mixed venous blood of lower oxygen saturation into the systemic circulation during and following the

TABLE III

Data Obtained from Right Heart Catheterization

NO.	DATE	NAME	SEX	AGE	SURF. AREA M^2	CC. O_2 CONS.	CC. CO_2 PROD.	R.Q.	MIN. VOL. L/M	B.M.R.	S.V.C. O_2 VOLS. %	R.A. O_2 VOLS. %	R.V. O_2 VOLS. %	P.A. O_2 VOLS. %	P.V. O_2 VOLS. %	P.A. O_2 VOLS. %	ARTERIAL BLOOD		CARDIAC OUTPUT		INTRA-CARD. SHUNT L/M/M^2	EFFECTIVE PULM. FLOW L/M/M^2	NO.
																	Cap. Vols. %	Sat. %	Pulm. L/M/M^2	System L/M/M^2			
1	4/ 8/46	J. S.	F	10	1.0	114	121	1.1	4.37	−32		15.8		19.2	22.2	19.0	23.1	83	3.65	3.44	.21 L-R	1.71	1
2	7/19/46	J. P.	M	39	1.7	187	164	0.9	8.4	−8		16.5	20.5	19.2	23.7	21.3	25.4	84	2.48	2.30	.18 L-R	1.53	2
3	11/15/46	E. S.	F	19	1.5	180	163	0.9	6.9	−6	13.7	14.0	15.8	17.7	23.0	18.5	24.2	77	2.20	2.60	.42 R-L	1.28	3
4	12/11/46	V. S.	F	25	1.5	205	200	1.0	9.3	+2	11.6	11.6	14.7	14.1	19.0	16.8	20.0	83	2.71	2.56	0.15 L-R	1.80	4
5	3/12/47	B. S.	M	9	0.9	111	113	1.0	6.0	−31	14.3	14.3	15.3	16.1	21.4	18.7	22.5	83	2.28	2.72	0.44 R-L	1.70	5

TABLE IV

Intraventricular and Peripheral Blood Pressures. Resistances in the Pulmonary and Peripheral Circulation

NO.	DATE	NAME	SEX	AGE	FEMORAL ARTERY MM. Hg			SYSTEMIC FLOW LITERS/MIN.	PERIPHERAL RESISTANCE DYNES-CM^5 PER SECOND	RIGHT VENTRICLE MM. Hg		PULMONARY ARTERY MM. Hg			PULMONARY ARTERY FLOW LITERS/MIN.	PULMONARY RESISTANCE DYNES-CM^5 PER SECOND	NO.
					Syst.	Diast.	Mean			Syst.	Diast.	Syst.	Diast.	Mean			
2	7/19/46	J. P.	M	39	120	75	90	3.9	1850					65*	4.2	1260	2
3	11/15/46	E. S.	F	19	134	82	102	4.0	2020	97	36	122	86	98	3.4	2300	3
4	12/11/46	V. S.	F	25	122	79	95	3.9	1920	112	0	112	64	80	4.2	1545	4
5	3/12/47	B. S.	M	9			100	2.5	3180	137	12			100	2.1	3800	5

* Mean pressure recorded with a saline monometer. All other pressures in this table recorded with the Hamilton Manometer.

exercise. Results obtained from catheterization of the right auricle, the right ventricle, and the pulmonary artery demonstrate that the pulmonary artery blood flow exceeds systemic blood flow by 180 cc. per min./M^2. This figure is too low to be considered an indication of a preponderant left to right shunt. On the other hand, the following observations indicate extensive interventricular admixture of blood: The oxygen content of pulmonary artery blood exceeds that of right auricular blood by 2.7 volumes per cent, and the effective pulmonary artery flow is 1000 cc. less than the volume flow through the pulmonary artery. These findings indicate large left to right currents. The reduction of the peripheral arterial oxygen saturation to 83 per cent, however, demonstrates that some of the interventricular currents are flowing from the right ventricle into the overriding aorta. The negligible value derived for the intracardiac shunt and the evidence for extensive interventricular admixture of blood make it probable that the volumes of the mixing currents from right to left and from left to right are about equal.

Case 3. E. S. (age 19 years, date of study November 13, 1946). The patient was supposedly normal at birth. When she was 4 years old her parents consulted a physician because she had begun to exhibit marked breathlessness with moderate exercise. At that time she was found to be slightly cyanotic at rest. Her condition had remained the same until she was 15 years old when shortness of breath became apparent during the slightest exertion. The shortness of breath could be relieved by squatting. Since then she had had spells of dizziness and palpitation which lasted several minutes at a time. There had been no episodes of hemoptysis.

On physical examination her lips were slightly cyanotic and there was minimal clubbing of the fingers and toes. There were no abnormal physical findings in the lungs. The heat was not enlarged on percussion. There was a slight systolic thrill felt over the base of the heart. On auscultation a very low pitched systolic murmur was heard. This murmur increased in intensity during mild exercise. No diastolic murmur was heard.

The red cell count was 6 millions per cmm. The hemoglobin was 17.5 gm. (Sahli). The volume of packed red cells was 57.3 per cent. The electrocardiogram showed right axis deviation in the standard leads and right ventricular hypertrophy in the chest leads.

On fluoroscopy the heart appeared to be of normal size. The pulmonary conus was full and expansile pulsations in the lung fields could be seen.

Physiological studies: Table II shows that the pulmonary capillary flow was within normal limits. However, it exceeded pulmonary

artery flow by 900 cc. The results of the standard exercise test are illustrated in Table I. It can be seen that the ratio of carbon dioxide produced per liter of ventilation fell from rest to exercise; the ratio of oxygen consumed per liter of ventilation, on the other hand, rose. The arterial oxygen saturation determined immediately following the exercise was considerably lower than the resting value. The significant

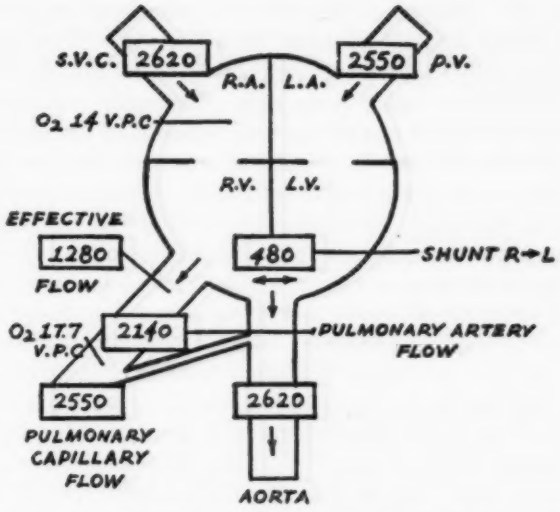

FIG. 1. ILLUSTRATES THE FINDINGS IN PATIENT #3 (E. S.) AGE 19.

It may be seen that the systemic flow exceeds pulmonary artery flow, giving the intracardiac shunt an overall direction of from right to left. The pulmonary artery, however, receives oxygenated blood from the left side of the heart, since the oxygen content of pulmonary artery blood exceeds the oxygen content of right auricular blood.

results obtained by catheterization of the heart may be summarized as follows (Fig. 1 and Table III): (1) The systemic flow exceeded pulmonary arter flow by 400 cc. (2) The effective pulmonary blood flow was 60 per cent of the pulmonary artery flow. (3) The oxygen concentration of the pulmonary arterial blood closely approached that of femoral artery blood, while exceeding that of right ventricular and auricular blood by 1.9 and 3.7 vol. per cent respectively (the right

ventricular sample was collected near the tricuspid valve). (4) The oxygen saturation in peripheral arterial blood was 77 per cent. (5) The pressures in the right ventricle were 97/36 mm. Hg, those in the pulmonary artery 122/86 mm. Hg. Pulmonary artery and right ventricular pressures were not recorded simultanously. This probably explains the difference in the height of the respective systolic pressures (Table IV).

Comments. The value obtained for pulmonary capillary flow is similar to that recorded in normal individuals (6). They exceed considerably, however, pulmonary artery flow, indicating the presence of some collateral circulation to the lung. The results obtained with the standard exercise test conform to those obtained in the previous cases. Since pulmonic stenosis is probably absent, the effective pulmonary blood flow can increase during exercise in proportion to the minute volume of respiration. This results in a rise in the ratio oxygen consumed per liter of ventilation. The findings obtained with the catheterization of the heart are illustrated in Table III and Figure 1. In contrast to the previous case, the systemic blood flow is slightly greater than that through the pulmonary artery, with the result that the overall direction of the intracardiac shunt is directed from right to left. On the other hand, the large difference in the oxygen content between blood from the right auricle and the right ventricle and the pulmonary artery respectively indicates that the pulmonary artery receives oxygenated blood from the left side of the heart. This conclusion is also supported by the fact that the effective pulmonary blood flow is 50 per cent that of the pulmonary artery flow. The aorta, however, receives a large amount of mixed venous blood. This is indicated by the reduced oxygen saturation of peripheal arterial blood.

The pressures recorded from the right ventricle and the pulmonary artery show an elevation of the systolic and diastolic pressures in the pulmonary artery and the right ventricle above their normal values. It is possible that the abnormally high diastolic pressure recorded in the right ventricle of this patient is the result of an insufficiency of the pulmonic valve, although clinical evidence for this is lacking.

Case 4. V. S. (age 25, studies begun December 9, 1946). The patient is said to have been blue at birth. She related that she had been short of breath as

long as she could remember. In 1943 she had had a normal full term pregnancy and since then had had repeated hemoptyses, which at first amounted to little more than blood streaked sputum; during the last year the hemoptyses had become more extensive, occurring characteristically during the ten to twelve days before the onset of menstruation. She had had her most serious hemoptysis a year before admission when she is said to have coughed up about a quart of fresh blood. Immediately following this she was admitted to a hospital where she remained for several days. Since then hemoptyses had not occurred. At the time of admission for study she had no complaints although her exercise tolerance was impaired.

On physical examination a slight degree of cyanosis of the lips was present. There was marked clubbing of fingers and toes. The lungs were normal on percussion and auscultation. The blood pressures in the arm (auscultation) were 120/75 mm. Hg. The heart was not enlarged to percussion and there was no thrill. A loud systolic murmur could be heard over the whole left anterior chest wall, with its maximum intensity at the left sternal border. No diastolic murmur was audible.

On fluoroscopic examination the right auricle and ventricle seemed to be enlarged. This was particularly apparent in the left anterior oblique position. There were flatness in the region of the pulmonary conus and increased vascular markings in both lung fields which showed definite expansile pulsations. The hemoglobin was 15.0 gms. per 100 cc. (Sahli). The red blood cell count was 5.4 millions per cmm. and the hematocrit was 49 per cent. The electrocardiogram revealed right axis deviation in the standard leads.

Physiological studies: The results of the standard exercise test are illustrated in Table I. Both the ratios carbon dioxide and oxygen produced and consumed per liter of ventilation increased during the exercise test. The peripheral oxygen saturation could not be determined, but it was observed that the cyanosis increased immediately following the exercise. Table II demonstrates that the pulmonary capillary flow was within normal limits and slightly exceeded the pulmonary artery flow. The results of catheterization of the heart are illustrated in Table III and Fig. 2. It can be seen that (1) the volume of blood flowing through the pulmonary artery was of the same order as that perfusing the systemic capillaries; (2) the effective pulmonary blood flow was considerably lower than the pulmonary artery flow; (3) the oxygen content of pulmonary artery blood exceeded that of right auricular blood by 2.5 vol. per cent; (4) the systolic pressure in the right ventricle was 112 mm. mercury (Table IV), which represents an elevation of approximately 80 mm. of Hg above normal ventricular

pressures recorded by Cournand (7). The blood pressures in the pulmonary artery were also increased (Table IV).

Comments. The rise in the ratio oxygen consumed and carbon dioxide produced per liter of ventilation obtained during the standard exercise test indicates that the effective pulmonary blood flow increases

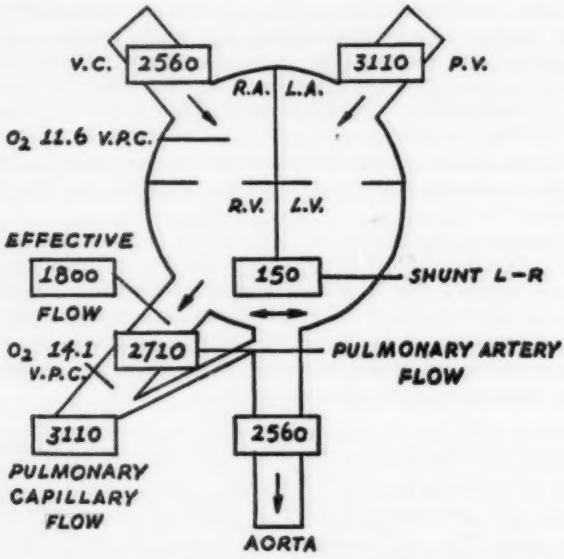

FIG. 2. SHOWS THE FINDINGS IN PATIENT #4 (V. S.) AGE 25

There is a slight preponderance of the overall intracardiac shunt from left to right. The observation that the effective pulmonary blood flow is less than the pulmonary artery flow and the finding of a large difference between the oxygen contents of pulmonary artery and right auricular blood indicate left to right mixing currents.

sufficiently to take care of the respiratory demands of exercise. The absence of significant collateral circulation to the lung is demonstrated by the fact that the difference between pulmonary capillary flow and pulmonary artery flow is small (Table II and Fig. 2). Similarly, as in the previous case, there is no preponderant direction of the interventricular mixing currents. This is indicated by the observations

that pulmonary artery flow almost equals systemic flow (Table III and Fig. 2). It is probable, however, that interventricular admixture of blood takes place. This assumption is supported by the following facts: The oxygen content of the pulmonary artery blood exceeds that of right auricular blood by 2.5 vol. per cent; the effective pulmonary blood flow is 1000 cc. less than the pulmonary artery flow, and the

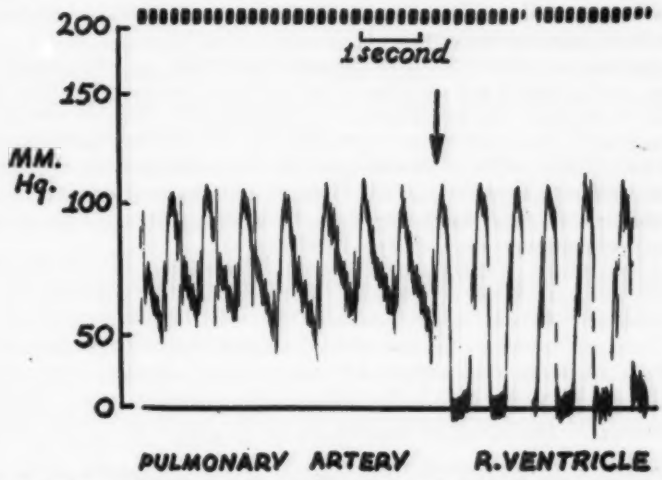

FIG. 3. ILLUSTRATES CONTINUOUS OPTICAL PRESSURE RECORDINGS OBTAINED FROM THE PULMONARY ARTERY AND THE RIGHT VENTRICLE OF PATIENT #4 (V. S.) AGE 25.

The record demonstrates high systolic and diastolic pressure in the pulmonary artery. Withdrawal of the catheter tip through the pulmonic valve into the right ventricle (arrow in figure) results in a sharp fall of the diastolic pressure to zero. The systolic pressure remains constant.

resting arterial oxygen saturation is below normal (Table III and Fig. 2). Of special interest are the blood pressures recorded from the pulmonary artery. As seen in Figure 3 and Table IV, the systolic and diastolic pressures in that vessel are greatly increased above the normal values of 25/8 mm. Hg which have been recorded from the pulmonary artery of normal individuals (7). The systolic pressure in the right ventricle is also greatly increased. The significance of these pressure readings and their diagnostic importance will be discussed below.

Case 5. B. S. (male, aged 9, date of study March 12, 1947). This patient appeared to be entirely normal at birth. At the age of four months his parents had noticed that his heart beats were unduly rapid. In the second year of his life blueness of the lips and fingernails had become apparent and had persisted ever since with increase in intensity on exertion. The child's activities had always been limited by shortness of breath. In the two years prior to examination there had been a gradual decrease in exercise tolerance so that at the time of entry the child could hardly walk a city block or mount a flight of stairs. There had always been a marked tendency toward contraction of respiratory infections. No history of hemoptysis could be elicited.

Physical examination: The child appeared underweight and the posture was poor. Mild cyanosis and clubbing of the digits were evident. The lungs were clear to percussion and auscultation. The area of cardiac dullness was not increased and a shock was felt over the precordium. The second heart sound was particularly loud in the fourth left interspace. A short harsh systolic murmur heard maximally over the third and fourth left interspaces could also be heard bilaterally in the interscapular regions. A diastolic murmur was not audible. The blood pressure in the arms was 110/90 mm. Hg.

Laboratory data: The red blood cell count was 5.75 millions per cmm, the hemoglobin 15.9 gms. (Sahli), the hematocrit 48 per cent and the arm to tongue circulation time (decholin) was 10 seconds.

Under the fluoroscope the heart seemed enlarged in both the anteroposterior and transverse diameters with the left ventricle more prominent than normal. Active pulsations were seen in the region of the pulmonary conus. The hilar markings were increased but active pulsations in the lung fields were not present.

Physiological studies: On performance of the standard exercise test both oxygen consumed and carbon dioxide produced per liter of ventilation remained approximately constant (Table I). The arterial oxygen saturation was not obtained immediately following the exercise, but it was felt that the patient showed a marked increase in cyanosis.

The pulmonary capillary flow, shown in Table II, was reduced to about 75 per cent of the average normal index. However, since it was equal to the pulmonary artery flow, collateral circulation was not present. Other data obtained from right heart catheterization are summarized in Table III which contains the following observations: (1) The flow through the systemic circulation exceeded that through the pulmonary artery by about 20 per cent, resulting in a right to left intracardiac shunt of 440 cc./M^2; (2) the oxygen content of the pulmonary artery blood was within 2 volumes per cent of that in the right auricle; (3) the effective pulmonary flow was only 75 per cent of the

flow in the pulmonary artery, and the peripheral arterial blood oxygen saturation was reduced to 83.4 per cent.

Pulmonary artery and peripheral arterial pressures, shown in Table IV, were dampened, hence only mean values could be derived from the tracings. In each case a mean pressure of 100 mm. of Hg was found. In the right ventricle a systolic pressure of 137 mm. of Hg and a diastolic pressure of 12 mm. of Hg were recorded.

Comments. The failure of the oxygen consumed per liter of ventilation to rise during exercise indicates that the effective pulmonary flow fails to increase normally during exercise (Table I). This observation is consistent with the finding that the pulmonary artery flow is reduced below the normal index (Table III).

Although the oxygen content of pulmonary artery blood is not greatly different from that in the right auricle, left to right admixture of ventricular blood must take place as the effective pulmonary flow is less than the pulmonary artery flow (Table III). The existence of right to left admixture is demonstrated by the lowered peripheral arterial oxygen saturation (Table III). There is a sufficient overall right to left shunt of 440 cc. (Table III)

The findings in this case resemble those in patient 3 (E. S,). As in case 3 the pulmonary artery flow is decreased and the overall direction of the intracardiac shunt is directed from right to left. In these respects the dynamics of both cases resemble those reported previously in tetralogy of Fallot (2). Pulmonic stenosis is absent, however, since the mean pressure in the pulmonary artery is elevated. In these two patients (B. S., #5, and E. S. #0) the calculated pulmonary resistance is considerably elevated (Table IV) and exceeds the peripheral vascular resistance. Consequently, in the absence of pulmonic stenosis, the predominent right to left intracardiac shunt must be the sequence of increased resistance in the smaller vessels of the pulmonary vascular tree.

DISCUSSION

The clinical histories of the 5 patients who are the subjects of this report reveal that dyspnea on ordinary exertion developed during childhood. Two of them had repeated episodes of hemoptyses. In case #4, V. S., the hemoptysis was so severe on one occasion that it necessitated hospitalization. On inspection, moderate clubbing of the

fingers and toes and mild cyanosis were found in all cases. On physical examination of the heart a systolic murmur was audible in every instance. No diastolic murmur could be heard. The lungs were clinically normal. Laboratory data revealed that the hemoglobin content varied from 15 to 19 gm. per 100 cc. of blood, the red cell count from 5 to 7 millions per cmm., and the hematocrit from 48 to 68 per cent. The electrocardiograms showed right axis deviation in 3 cases. One patient (J. P., #2) had left axis deviation. On fluoroscopic examination, expansile pulsations in the lung field were seen in 4 of the 5 cases. Fullness of the pulmonary conus was present in 4 patients. In one case (V. S., #4) the pulmonary conus was not prominent.

An analysis of the physiological data demonstrates that the performance of the standard exercise test was accompanied in 4 out of 5 cases by a rise in the ratio of oxygen consumed per liter of ventilation (Table I). In one patient (B. S., #5) it remained constant. This finding contrasts with that obtained in most patients with tetralogy of Fallot, in whom this ratio declines during exercise (2). The rise in this ratio furnishes evidence that the effective pulmonary blood flow can increase during exercise. In tetralogy of Fallot, pulmonic stenosis limits the effective pulmonary blood flow during exercise and the ratio oxygen consumed per liter of ventilation declines (2). The oxygen saturation in the peripheral arterial blood fell in 3 cases, as it did in tetralogy of Fallot (2). In the other 2 cases, in whom the arterial oxygen saturation was not obtained, cyanosis was visibly increased after exercise. It is probable that this is the result of increased shunting of venous blood into the overriding aorta, shunting of venous blood with lower oxygen saturation, or a combination of both. The physiological data obtained with the standard exercise test, therefore, reveal the importance of this test in differentiating cases with adequate pulmonary flow from those in whom pulmonary blood flow is decreased. Consequently, it has been of value in the preoperative selection of patients for operation.

In 2 patients (E. S., #3, and V. S., #4) the pulmonary capillary blood flow was within normal limits (6). In 2 others (J. P., #2, and B. S., #5) the pulmonary capillary flow was slightly decreased, while in J. S. (#1) it was above normal. Table II indicates that in 2

patients (J. P., #2, and B. S., #5) values for pulmonary capillary flow approached those obtained for pulmonary artery flow, indicating the absence of significant collateral circulation to the lung. In 3 individuals (J. S., #1, E. S., #3, and V. S., #4) some increase in the collateral circulation to the lung was present, since pulmonary capillary flow exceeded that through the pulmonary artery. It is impossible at the present moment to ascertain why some individuals of this series have collateral circulation while others have not.

A comparison of the values obtained for pulmonary artery flow and systemic blood flow shows that the pulmonary artery flow slightly exceeded the systemic blood flow in 3 cases (J. S., #1, J. P., #2, and V. S., #4) (Table III and Fig. 2). These findings indicate that in these patients there is a slight preponderance of the intracardiac shunt toward the right. In E. S. (#3) and B. S. (#5), however, the overall direction of the intracardiac shunt was from right to left since the systemic flow was larger than the pulmonary artery flow (Table III and Fig. 1). Irrespective of the overall direction of the intracardiac shunt, interventricular mixing currents existed in all patients. Left to right admixture is indicated by the relatively high values for the oxygen contents of pulmonary artery blood and by the low values obtained for effective pulmonary blood flow. On the other hand, the decrease in the peripheral oxygen saturation demonstrates the presence of right to left currents.

These observations are of considerable interest since they permit certain assumptions to be made concerning the nature of pulmonary hemodynamics. If the total cross-sectional area of the pulmonary arteriolar bed were normal in the absence of pulmonic stenosis, the intracardiac shunt would be predominantly directed toward the right. The preceding discussion indicated, however, that in 3 patients the overall volume of blood shunted from left to right was insignificant. In 2 individuals there was a significant right to left shunt. In all instances pulmonic stenosis was absent since both systolic and diastolic pressures in the pulmonary artery were elevated. These observations indicate, therefore, an increase in the vascular resistance of the pulmonary bed.

This conclusion is further substantiated by the pressures recorded from the pulmonary artery (Table IV). It can be seen that in all

of them the mean pressure in this vessel is elevated above normal values. In E. S. (#3) and V. S. (#4), in whom systolic and diastolic pressures were recorded, both pressures are increased (Fig. 3). It is probable that in the presence of normal blood flow the elevation of the diastolic pressures above normal values of approximately 8 mm. Hg (7) represents the result of increased resistance in the pulmonary bed. This assumption is supported by the findings represented in Table IV. It is seen here that the calculated resistance in the pulmonary vascular tree is increased considerably over the normal of 300 dynes/cm^5/sec.[1] In 2 patients (J. P., #2, and V. S., #4) the pulmonary vascular resistance is slightly below the peripheral resistance. In 2 cases (E. S., #3, and B. S., #5) the pulmonary resistance exceeds the peripheral resistance.

The increase in the resistance in the pulmonary bed is also illustrated by changes which occur in the energy expended by the right ventricle of these patients. It is realized that in addition to the assumptions usually made in the calculations of the work of the normal heart, further assumptions have to be made in the cases under discussion. This will greatly detract from the accuracy of the results obtained. Nevertheless it is felt that the calculation of the work of the heart might further contribute to an understanding of the principal hemodynamic changes in this complex disease.

It is customary in the calculation of the work of the heart to distinguish between velocity and pressure energy (10). Since the velocity energy is usually small, and since its calculation is based on figures of doubtful accuracy, it is usually neglected in the estimation of the work of the heart. In the cases discussed in this paper the relative changes between velocity and pressure forms of energy are of importance. Therefore it has been necessary to calculate both forms of energy.

In these calculations the components for pressure and velocity energy are computed with reference to the aorta and the pulmonary artery only. No attempt is made to include the energy contents of the blood passing through the interventricular septal defect. The

[1] The figure of 300 dynes/cm^5/sec. was derived from an application of Aperia's formula (9), using accepted normal values for cardiac output and mean pulmonary arterial pressure.

facts which would permit these calculations are too difficult to ascertain. Furthermore, the volume of the overall intracardiac shunt is too small to make the energy contents of the blood shunted through the defect significant.[3]

The chief assumptions made in calculating the energy relationships were the crosssectional areas of the aorta and the pulmonary artery. The figures for crosssection areas used were compiled from normal autopsies (11). It is conceivable that in the patients who form the subject of the present discussion the pulmonary hypertension led to an increase in the crosssectional area of the pulmonary artery over the normal. Another difficulty in evaluating the data obtained arises from the fact that the energy expenditure of the heart varies directly with the cardiac output and the mean blood pressure and indirectly with the crosssectional area of the large vessels. It is known that all these factors are determined by individual characteristics such as age and sex. Consequently, it is difficult to interpret the values obtained

[3] The formulae used in the calculation of the work of the ventricle are derjved from Starling (10).

(1) Pressure energy (Gram-cms.) = M.P. × S.D. × D. Hg.

where M.P. = Mean Blood Pressure in the pulmonary artery or aorta (mm. Hg)
S.D. = Systolic Discharge (cc./min.)
D. Hg = Density of Mercury

$$(2) \qquad \text{Velocity energy (Gram-cms.)} = \frac{V_A \times S.D.}{2g}$$

where V_A = Velocity of blood in pulmonary artery or aorta (Cms./sec.)
S.D. = Systolic Discharge (cc./min.)
g = gravity constant

V_A The flow velocity in the pulmonary artery or aorta was calculated according to the formula:

$$(3) \qquad V_A \text{ (Cms./sec.)} = \frac{SD}{C_A \times ET}$$

where S.D. = Systolic Discharge (cc./min.)
C_A = Cross Section area of pulmonary artery or aorta (Cms^2)
ET = Systolic Ejection period (sec.)

The systolic ejection period was calculated according to the formula:

$$(4) \qquad \text{Systolic ejection period (sec.)} = \frac{60/\text{Pulse rate}}{8/3}$$

$$(5) \qquad \text{Systolic discharge (cc./min.)} = \frac{\text{Minute volume (cc min.)}}{\text{Pulse rate (beats per minute)}}$$

for velocity or pressure energy by relating them to normals. Some conclusions, however, may be drawn by relating the velocity energy of each ventricle to total work and by comparing the work of each chamber with that of the whole heart. These relationships can then be compared with those existing in the normal.

It may be seen in Table V that in the right ventricle of the 2 patients the ratio $\frac{\text{velocity energy}}{\text{total work}}$ is one tenth of the normal. Normally the ratio $\frac{\text{velocity energy}}{\text{total work}}$ is 5 times as great in the right ventricle as in the left (Table V). In the 2 patients, on the other hand, this ratio is reversed, being greater in the left than in the right ventricle. This is to be expected since normally the right ventricle is not working against high pulmonary resistance. Similar calculations made for the ratio $\frac{\text{velocity energy}}{\text{total work}}$ of the left ventricle approach normal values (Table V). This demonstrates that the energy expenditure of the right ventricle in overcoming pulmonary resistance is proportionally as large as that expended by the left ventricle in the overcoming of peripheral resistance.

The last column in Table V illustrates the relationship of the total work of the right ventricle to that of the whole heart. It can be seen that normally the right ventricular component is small compared to that of the whole heart. In the 2 cases illustrated in Table V, however, the work done by the right ventricle comprises almost one third to one half of that of the total work of the heart. It is evident that the increase in the ratio right ventricular work to that of the whole heart is the result of increased resistance in the pulmonary bed. This forces the right ventricle to raise the pressure energy expenditure in order to maintain adequate blood flow through the lung. It is difficult to ascertain the anatomical lesion responsible for an increase in pulmonary resistance since reports of the microscopic pathology of lung tissue in congenital heart disease with increased pulmonary arterial pressure have not been published. Burnett and White (12), however, report endarteritic changes ln the pulmonary arterioles in 2 cases of large interauricular septal defect. It is conceivable that similar lesions exist

TABLE V

The Work of the Heart in Two Cases of Eisenmenger's Complex

NO.	DATE	NAME	SEX	AGE	RIGHT HEART										LEFT HEART										TOTAL WORK OF WHOLE HEART	WORK OF RIGHT / TOTAL WORK OF WHOLE HEART × 100	NO.
					Systol. Discharge cc.	Cross sec. Area Cm^2	Systol. Ejec. Time Seconds	Velocity Cm./Sec.	Velocity Energy Gm.-cms.	Pressure Energy Gm.-cms.	Mean Pressure mm.Hg	Total Work Gm.-cms.	Vel. energy / Total work × 100		Systol. Discharge cc.	Cross Sec. area $Cm.^2$	Systol. Ejec. Time Seconds	Velocity Cm./Sec.	Velocity Energy Gm.-cms.	Pressure Energy Gm.-cms.	Mean Pressure mm.Hg	Total Work Gm.-cms.	Vel. energy / Total work × 100				
*Normal					66.5	5.14	.3	43	1.46	1360	15	1361.5	.11		66.5	3.9	.3	37.0	1.94	9050	100	9051.9	.0214		10413.0	13	Normal
3	11/15/46	E. S.	F	19	36.7	5.14	.25	28.4	.53	4850	98	4850.5	.011		44.5	3.9	.25	46.0	1.04	6200	102	6201	.0162		11051.5	43.5	3
4	12/11/46	V. S.	F	15	46.0	5.14	.25	35.7	.84	5000	80	5000.8	.017		50.5	3.9	.25	52.0	1.35	6500	95	6501	.02		11501.8	43.5	4

* Values for the work of the normal heart were derived from the following figures:
minute volume = 5000 cc./min.; pulse rate = 75/mm.; cross section area of pulmonary artery = 5.14 cm^2.; cross section of aorta = 3.9 cm^2. Mean pressure in pulmonary artery = 15 mm. Hg. Mean pressure in aorta = 100 mm. Hg.

in the cases reported in this paper. Unpublished observations from the Department of Pathology of the Johns Hopkins Hospital on several cases of dilatation of the pulmonary artery with septal defects in infants have demonstrated generalized narrowing of the lumina of pulmonary arterioles due to thickening of the media and intima. Of special significance were the findings that the pulmonary alveolar walls were normal (13).

The results obtained from the study of the patients discussed in this series make it apparent that these cases belong both clinically and physiologically to a common group, which has been designated "Eisenmenger's complex." Gross pathological observations make it clear that this complex is distinguished from the tetralogy of Fallot by a normal or dilated pulmonary artery (4). Quantitative physiological observations of this disorder have not been published to our knowledge. In his original paper Eisenmenger assumed that the intracardiac shunt was predominantly directed from left to right. The results described in this paper indicate that Eisenmenger's complex is characterized by pulmonary hypertension, by normal or reduced pulmonary artery flow, and by a reduction in the effective pulmonary blood flow. The resistance in the pulmonary vascular tree is increased and the intracardiac shunt is directed both from right to left and from left to right.

SUMMARY

Five cases of Eisenmenger's complex have been studied.

The performance of the standard exercise test was accompanied in 4 out of 5 cases by a rise in the ratio of oxygen consumed per liter of ventilation. The ratio remained constant in one patient. These findings are in contrast to those obtained in patients with tetralogy of Fallot, in whom the ratio oxygen consumed per liter of ventilation usually declines.

In 3 patients there was a slight preponderance of the intracardiac shunt from left to right. In 2 patients the overall direction of the intracardiac shunt was toward the left. Irrespective of the overall direction of the intracardiac shunt, interventricular admixture of blood existed in all cases.

Increased resistance in the pulmonary bed was indicated by the following findings:

a. A left to right intracardiac shunt was either small or absent.

b. Both systolic and diastolic pressures in the pulmonary artery were elevated.

c. The ratio $\frac{\text{velocity energy}}{\text{total work}}$ calculated for the right ventricle was one tenth of the normal, and the work of the right ventricle comprised one third to one half of the total work of the heart.

The relationship of these findings to clinical observations was discussed.

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THE IMPACT OF MODERN PSYCHIATRY ON MEDICAL EDUCATION, MEDICAL PRACTICE, AND HOSPITAL ORGANIZATION

LAWRENCE S. KUBIE, M.D.

The class which graduated from the Johns Hopkins Medical School in 1921 has been unique with respect to the number of graduates who have become psychiatrists. Five of us interned in the Phipps; and since then several others have joined our ranks. This must have something to do with the fact that I was selected to represent the class at this reunion. It is an honor and an opportunity which I appreciate deeply; but there are many others in the class who in the intervening quarter-century have made more significant contributions to medical science than I have.

I am embarrassed at the somewhat grandiose scope of the title of this paper. On such a topic there is either very little to say, and that quite obvious, or else so much to say that one could talk for hours. I want to talk to you slowly for emphasis, because I feel deeply about these matters; and on the other hand I want to talk as rapidly as I can in order to cover as much ground as possible. I remind myself of a patient who talked so rapidly that I could barely understand him. One day he suddenly caught his breath and said, "The reason I talk so fast is so that I can get my money's worth." To be here today, with the privilege of presenting to you certain views which I have developed over the years, is more than my money's worth. And since it would take a hundred minutes instead of thirty to cover this subject, I will begin by wasting a few moments by referring briefly to two basic issues which I cannot discuss fully.

There are two problems in the structure of medicine, the solution of which is a necessary prelude to a happy marriage between psychiatry and organic medicine: the economic organization of medicine, and the emotional immaturity of our educational system. With more time it would be easy to demonstrate that economic insecurity stands between psychiatry and organic medicine, turning initial eagerness into rivalry, fear, and hostility. Similarly psychological immaturity converts initial interest into outrage and incomprehension. For

these basic problems the only cure is a sounder social and medical economy, and a more mature educational system from the nursery years on up. An adequate discussion of these topics is beyond the scope of this brief paper.

Nor will I give you the speech which is expected of a psychiatrist when he addresses a group of internists and surgeons. I will give you no defense of psychiatry. I will present no illustrative case histories. I will assume that you have heard all of this many times; and that in theory we are in agreement about the deepening part that psychiatry is destined to play in modern medicine. Instead, on the strength of that comfortable assumption, I will go directly to my theme.

In the 25 years which we celebrate today psychiatry has changed far more than is generally realized,—changed even more than these familiar halls. For a primary preoccupation with the psychoses it has substituted a primary preoccupation with the neuroses. True there are 600,000 overcrowded beds for psychotic patients in the country; and as many more patients on parole or in remissions or discharged as socially adjusted. This however is nothing compared to the numbers of human beings with frank symptomatic neuroses, variously estimated in this country as between 6 and 12 millions: estimates which are conservative when we take into consideration the masked personality neuroses as well, a group which it will be my argument that medicine can no longer ignore.

This shift in the field of work of the psychiatrist creates a large and difficult challenge for all of medicine. To understand its full implications we must stop for a moment to consider how it has come about. As always in medicine changes result not from new words, but from new techniques and their courageous and dogged if blundering application. The technique that has wrought this change is psychoanalysis: because it was our first method for a systematic exploration of conscious and unconscious levels of the personality. This is not to say that psychoanalysis is a perfect instrument, or that it is the ultimate answer. Far from it. In his own summary of psychoanalysis in the 1926 edition of the Encyclopedia Britannica, Freud himself said explicitly that in the long and retrospective view of science, psychoanalysis will be seen to have been important not as a technique of treatment but as a first approach to a scientific understanding of

human nature. This understanding has been won through bitter and often heart-breaking struggles to analyze the neurotic process, both in those states of decompensation which we call neuroses, and in the masked neurotic process which influences the daily lives of all of us. There will be better and briefer methods of treatment; but it is worth a word of warning that we do not possess them yet, that although we are working on them and moving towards them, premature claims should be heard with careful scepticism. . . .

In the meantime the study of human nature, like the study of physiology, proceeds from the investigation of pathological deviations (i.e. neuroses) to the study of the normal. Here again, psychiatry is recapitulating the history of medicine in general. Twenty-five years ago in these United States only about 50 men were attempting to deal with the neuroses, either in private practice or in community agencies. Of these 50 about 20 called themselves analysts, only a few with any real right to the name. Today there are nearly 400 well-trained analysts in the country. In New York City, 125 physicians are members of the New York Psychoanalytic Institute which is training about 120 physician-students: and nearly 150 applications are on file for next year, largely from veteran medical officers. This is an indication of the change which is in progress within psychiatry itself. When I think of the past I am amazed at the change in our medical and cultural outlook which has been started by these few students of human nature and its subtle pathology. I am tempted to paraphrase Churchill and say, "Rarely in the history of medical science has so much been owed to so few."

At the same time I might add that I am also amazed by the persistent power of the neurotic forces in human nature which make it so difficult for us to learn either from our own experiences or from those of others. Again and again medical schools which made obvious and predictable blunders in their choices of psychiatric leaders a quarter of a century ago, today are repeating these errors by placing the choice in the hands of those who are devoid of any understanding of the needs of modern psychiatry, and who are actively hostile to psychiatry, or into the hands of those who still think of psychiatry in terms of the psychoses. As one who spent many precious years making himself respectable on psychiatric wards, in the laboratory and in organic

neurology, let me say quite explicitly that valuable though all of that may have been to me in my own emotional development, I did not begin to start to become a psychiatrist worthy of the name until I began the analytic study of the neurotic process. For this there is no substitute! Men who know all there is to know about the psychoses may still be ignorant as babes about human nature and the neuroses. From his army experiences, William C. Menninger could verify this many times over.

Furthermore, clinical maturity comes slowly to the psychiatrist. In internal medicine or surgery the house officer can see thousands of patients in a year. Not so in the study of the neuroses. Consequently, even though one learns a great deal from the intensive analytic study of a few patients which is broadly applicable to many, it takes 10 to 15 years to acquire in psychiatry the broad clinical experience that can be gained in a few years in other medical fields. I will say quite frankly that I am not proud of many things in my life; but I am proud that many years ago I had the clarity and courage to refuse several enticing academic offers which would have permanently stunted my own development by swamping me with teaching and administration and by making it impossible for me to secure analytic training and experience. And I know several other men who have had to make the same choice. In no other field of medicine do we pay as high a price as in psychiatry for burdening immature and promising young psychiatrists with academic honors which prevent their further growth.

I mention these otherwise unimportant personal experiences only because I believe that they point up a general lesson. They mean, if they mean anything, that we must re-examine our ideas of how to train psychiatrists, and of who should be trained. To this I will return later.

First, however, since everything I have to say centers around the neurosis, I would ask you to consider with me the significance of three crucial facts about the neurotic process: (1) that it is actually and in reality universal; (2) that it can and does co-exist with every other medical and surgical ill to which we are heir; and (3) that it is so often masked.

Its universality means that that preventive psychiatry of which we

have all heard so much and seen so little must somehow be made a living reality in our culture and in the medicine of the future.

Its co-existence with organic disease means that there is need for far more extensive and intensive psychiatric service in all hospitals and clinics and private offices than has ever been contemplated in the past, with far larger staffs of psychiatrists than you now conceive.

Its masking means that screening and sifting devices and personnel trained to use such devices must be made available for this work in many areas of life; not only in hospitals, but also in schools, industry, social agencies, and government.

First, then, what can we say about prevention? Over the years we have all heard much about mental hygiene and preventive psychiatry, much talk with little achievement. In the main this is because there has been no such thing as early treatment. Prevention could mean much more than treatment: but that which can be done in the nursery or in the community to prevent neuroses requires a population which is emotionally more mature, better instructed, more informed, and freer from bias and bigotry than exists. Taking the world as it is today, prevention means primarily one thing: to treat every flurry of psychiatric symptoms as a medical emergency. This means early treatment of every transitory neurotic episode of childhood. It means treatment of the adult before neuroses become fixed and irreversible. Psychiatry must cease to be always too little and too late.

Neuroses constitute the largest medical problem in the world; more universal even than a common cold in the midst of an epidemic. The so-called "neurotic" explosions of childhood are inevitable developmental episodes in the life of the normal infant and child. That which we call a psychoneurosis is merely a symptomatic crisis, a transitory or persistent period of decompensation in the course of an incessant struggle, one that goes on in every human being throughout his life, a struggle between normal and neurotic forces. The neurotic process is active in every one of us from birth to death. For the most part, it is masked, manifesting itself in our personalities, in our ways of living and working, of loving, of building families. We live not by a series of free choices but by a sequence of automatic compromises between unconscious forces and conscious forces which are engaged in a process of conflict and compromise inside of us. The neurotic epi-

sodes of infancy, childhood, and of early adolescence are the earliest crises in this conflict, moments in which the unstable dynamic equilibrium tilts in one direction or another. To handle these episodes in the traditional fashion by discipline, argument, and exhortation, by rewards and punishment, by harshness and terrorization, may drive the conflict underground but cannot resolve it. And unless the underlying conflicts are resolved, out of each such episode of psychic decompensation, the child carries a residual scar of buried tensions which limit his flexibility and his capacity to adjust to the next period of strain in his life. If, on the other hand, these early neurotic episodes are treated promptly and intensively then the conflicts can usually be resolved so completely that the individual is left with no residual difficulty, and goes on his way through life strengthened and free. This is why the use of early therapy in childhood constitutes preventive psychiatry for the adult, freeing the grownup from the crippling after-effects of the neurotic episodes of childhood. Therefore the treatment of the child and adolescent is proving to be one of the most rewarding of all experiences in medicine from the point of view of the individual; and if more widely used it can be the source of hope for a greater emotional maturity in our whole culture. Thus although the realization that neuroses are universal at first seemed dismaying, its ultimate implications offer us our best and perhaps our only hope for the future of the human race. If greed and discontent and hatred and fear are manifestations of a universal illness which can be prevented by early treatment, then we may someday conquer them; not by religion and the arts, but by science.

The next preventive step would seem to be the invasion of psychiatry into the general hospital. This, however, is worse than useless when it is as half-hearted and as under-staffed as is usual. Early treatment requires early diagnoses of incipient neurotic difficulties, diagnoses based on positive evidence and not merely on exclusion of the organic. This in turn, when applied on a large scale, means psychiatric screening. Our services learned the importance of this. The British learned it when they screened the 21st Army Group for combat before D Day. They learned it when they screened repatriated prisoners of war for return to civilian life. They learned it in the War Office Selection Board which screened candidates for officer

training school by methods not unlike those used later, and partly borrowed, by our own Office of Strategic Services.

There is evidence that psychiatric screening of initial admissions would make possible quite sizable economies in clinic and hospital practice, and ultimately in hospital re-admission rates. The percentage of unrecognized and untreated psychoneurotics among the repeaters in out-patient and hospital practice is extremely high. In hospitals therefore one of the first requirements is an adequate screening system. Such a system implies that a psychiatric appraisal should be made early in the examination of every patient, and before subjecting him to every last organic examination which could possibly throw any light on his illness. This runs counter to current practice, which tends to exhaust the possibilities of organic investigation before attempting to find out what kind of a human being the patient is.

This change in procedure would save more than time and money. The battery of organic procedures may subject patients to serious and even irreversible psychiatric damage, confirming unspoken convictions and fears that something physical must be wrong. The patient who has not been carefully prepared often feels that the doctors would not put him through so many uncomfortable, expensive, and time-consuming tests "if nothing was wrong with me." The mere fact that the results of the tests are negative means little to the patient, compared to the emotional experience of being subjected to so many examinations. The doctor comes out of the orgy of tests with the conviction that the patient is physically sound; but the patient emerges with a deep belief that he has a mysterious ailment the nature of which the doctor is hiding from him. If psychiatry becomes part of the initial screen which greets every patient when he is admitted to a general hospital, to an out-patient dispensary, or when he enters the office of the private internist or surgeon, and if all invidious distinctions are avoided by making the psychiatric examination as routine a part of the initial evaluation of every patient as is the general inspection which initiates the physical examination, or the determination of blood pressure, hemoglobin, and urinalysis,—then much of the waste motion of traditional practice could be avoided, and patients could be spared a great deal of confusion.

In practical consequences what does this mean?

For several years before the war I ran a psychiatric service in a general hospital (Kubie, 1). This was not merely a consultation service on call from ward to ward, leaving behind a trail of interesting but unused diagnoses. We set up our psychiatric service only where we were invited, and only where we were allowed to install a three-man psychiatric team as a permanent and integral part of the ward. Each psychiatric team consisted of a mature psychiatrist who had had several years of experience in the analysis of the neuroses, and under him a couple of younger analysts. Gradually as we worked along, one service after another throughout the hospital asked us to install similar units; until we had ten teams, or thirty psychiatrists, working throughout the hospital. Everywhere we had the same experience. We would begin by seeing 1 to 2 per cent of the ward population. Within six months we would be called upon to see between sixty and seventy per cent, plus many of the doctors and nurses. Indeed our colleagues used to complain at the numbers of nurses and house officers who had previously been heading towards other specialties and who now planned to become psychiatrists.

It became evident that more universally and more subtly than is realized, neurotic discontent finds a safe and happy refuge in physical illness. Just as most women are happiest in the refuge of pregnancy, so the average human being, unless he has a specific phobia of disease is actually happier when he has measles or a broken leg then when he is facing himself and the world without such an alibi. This may be true even when the illness involves great pain. Physical ailments thus serve unconscious psychological purposes identical with those of the simulated illnesses of a conversion hysteria or of other psychopathological conditions, enabling the patient to hide from emotional difficulties. So generally true is this, that we learned to be suspicious of any patient who made too comfortable an adjustment to life on the hospital ward. We learned a lesson which the army never quite accepted, namely that the model patient of the army hospital all too frequently becomes the chronic repeater of the Veterans Administration. Somewhat reluctantly therefore we faced the fact that on every ward of every hospital in every bed lies a human being who is caught in conflict between normal and neurotic life forces, a conflict from which in many instances he achieves a transitory and deceptive peace

of mind through the welcome disguise of physical illness. This in turn brings us up against the unwelcome fact that convalescence is rarely an unmixed blessing (Kubie, 2). For most men convalescence means rather a return to those lives of quiet desperation which Thoreau ascribed to all of us. Once we grasp this, it becomes our duty as physicians to bring to the surface and to treat the masked neurosis in the convalescent just as carefully as we treated his more obvious broken leg. Instead, as things go today, just as soon as the bone is set we are only too glad to dismiss our patient as "cured", returning him to his purgatory with a sigh of relief at getting him off our hands and off our wards. In the not too distant future, we may discharge our patients through convalescent pavilions where their emotional needs will receive care as expert as their broken bones.

Thus psychiatry in our hospitals can do three things: (1) It can screen at the admitting office; (2) It can treat both the patient in the hospital, and his home through the psychiatric social service of the hospital; (3) It can prepare him for the strain of a return to health. The same functions can be played by the psychiatrist in a general private practice: but only if a true partnership is created between the psychiatrist and the internist or surgeon in their private offices, identical to that which is needed in hospital organization. This partnership will have to be financial as well as scientific, if it is to meet this problem squarely.

There are many other areas of life in which psychiatry is needed, areas which do not come strictly within the province of medicine, but which complicate our problem by the demands they make on our educational facilities. Psychiatric knowledge is needed in courts, schools and colleges, in social agencies, in industry, in the introduction of young people to the problems of marriage and of child-raising (Kubie, 4). Some believe that psychiatry may even be of importance for the understanding of economic, social and governmental problems, and in dealing with the origins of inter-racial strains and international hatreds.

How many psychiatrists do we need to perform all of these tasks? If psychiatric problems confront us with significant diagnostic and therapeutic problems in 60–75 per cent of all medical practice, do we need one psychiatrist for every internist and surgeon? Fortunately

not: but it is a conservative estimate that we do need at least 30,000 men and women trained in psychiatric knowledge and technique. Where are they to come from? Kubie, (3.)

No matter how well trained he is to a psychosomatic attitude, it is not likely that the busy practitioner will ever be able to be his own psychiatrist. Even if new methods materially shorten the duration of treatment, individual psychotherapeutic sessions have to be long. Therefore, just as it is impossible for a psychiatrist or a brain surgeon to undertake general medical responsibilities, conversely, the busy doctor or surgeon cannot devote several hours out of his day to the treatment of a few patients, because to do this would interfere with too many of his other professional responsibilities. Consequently, even if the internist or surgeon could acquire the necessary psychotherapeutic techniques, the time requirements are such that he could not often serve as his own psychotherapist. Indeed experience shows that when he undertakes to do his own psychotherapy, the pressure of other professional obligations usually forces the internist or surgeon to use superficial techniques which relieve symptoms temporarily but obscure the underlying neurotic process. This, thereupon, goes on unchecked until it breaks out later in more serious form. The psychiatrist frequently sees patients to whom this has happened, especially among the patients of those internists and surgeons who are most sympathetic to psychiatry, and who therefore attempt psychotherapy on their own.

This still leaves us to face the problem of where these vast numbers of men trained in psychiatric and psychotherapeutic techniques can be recruited or trained. We know that after 1910, the drive to raise the level of medical education cut in half the number of medical schools and medical students, and that the relative number of medical students has never since caught up to the growth of the population. Nor is there any indication that our facilities for medical education will increase rapidly enough even to take care of the need for more internists and surgeons, much less to take care of this need for vast numbers of additional psychiatrists. As I have said, we need 30,000. We have 4,000; of whom 3,000 work in hospitals and only about 1,000 in community agencies and private practice. We turn out about 75 a year: barely enough to balance the annual loss from disability, old age, and

death. How can we make up this deficit? There are only four alternatives, and these are not in any sense mutually exclusive: (a) by bringing up people so free from neuroses that they will not need psychiatry; a shining goal, but hardly of immediate help; (b) by training surgeons and internists to be their own psychotherapists; as we have seen, a plan that is not likely to work well; (c) by training more psychiatrists in our regular postgraduate medical curriculum; an essential step, but one which is limited by reason of the fact that the training takes about twelve years after graduation from college; (d) finally, by training a new para-medical profession, a doctorate in medical psychology and psychotherapy.

It is sometimes argued that our medical schools and teaching hospitals should take under their wings the development of a new paramedical specialty, creating a new doctorate in medical psychology, in which men could be trained in six to seven years after a Masters degree in academic psychology, these years to include clinical apprenticeships both in general and in psychiatric hospitals. This would save about half the time which it takes to train a medical psychiatrist, thus increasing both the number of trained individuals, and the number of years each man would have in which to use his special knowledge. This would make treatment available at lower cost both to individual patients and to the community; since training which takes only five to six years can be supplied at less expense than a training which takes ten to twelve years. Clearly, the pros and cons of such a solution should be carefully considered.

On philosophic grounds, the understanding of the psychological instrument by which humans live cannot remain the exclusive field of a small band of specialists. Instead, it must become the core of our educational process; and only the specific techniques of therapy will remain the special preoccupation of the psychiatrist. The ancient Greek admonition to "Know thyself" remained an empty hope until techniques came into our possession for penetrating to the unconscious neurotic forces that determine so much of the surface of our lives. On practical grounds, if we believe that psychiatric training is important not only in medical installations but also in so many other areas of life, then clearly it will never be possible to supply all of the trained medical psychologists and psychotherapists out of the medical profession alone.

Furthermore, it might be well to keep in mind the fact that events are moving forward under the pressure of a universal human need which will not be denied. It is putting our heads in sand to pretend that we can prevent the development of some such new discipline by standing up resolutely and saying that nobody without a medical degree should ever perform any psychotherapeutic functions. Today, all over the country thousands of so-called clinical psychologists are being trained for this very purpose, but with no medical supervision or training, entirely outside of the atmosphere and tradition of therapeutic responsibility which is found in teaching hospitals and medical schools, with wholly inadequate clinical grounding, and without direct first-hand familiarity with any of the phenomena either of organic or of psychiatric illness. To shut our eyes to this is folly; and to refuse to accept responsibility for training in this field will result in the country's being flooded by people who are inadequately trained.

It is not within the scope of this paper to present a detailed analysis of what elements of the medical curriculum would be retained in the training of such a para-medical specialty, and which could be eliminated. Careful study of the curriculum indicates, however, that out of approximately 6,000 hours in the entire medical curriculum, at least one-third could be eliminated to meet the needs of a curriculum in medical psychology by devoting them to psychological and psychiatric issues. That any such plan would create difficult problems with regard to space, staffing, and financing is obvious; but the fact that the problems are difficult does not mean that they are insoluble.

The existence of a para-medical curriculum in medical psychology within the framework of our medical schools would ultimately exercise a profound reciprocal influence on medical education. The anatomy and physiology of human personality, its inter-relation with social and economic stress, and their combined influence on organic and psychiatric disease would become a part of the curriculum for medical students from their first days in school; and medical science would then become in fact the three-legged stool described so aptly by Stanley Cobb, standing firmly and equally on internal medicine, surgery and psychiatry.

There will always be a function for the medically trained psychiatrist; but the psychiatrist alone cannot be the exclusive guardian of the mental health of a whole people, in dealing with problems which

affect 130,000,000 people, and which include every aspect of their relationship to one another, and every stage in their development. Instead, those who are trained in a new para-medical psychology, widely dispersed throughout the entire life of the community, might well become a starting point for a profound cultural evolution. And at the same time within our hospitals and medical schools, through a process of healthy cross-fertilization, they might exercise a maturing influence on our medical students, and—I might add—on our medical faculties.

This whole idea has its roots in the psycho-biology which is so familiar to us here. Two levels of integration, two overlapping but not coextensive areas of scientific knowledge, and two technical systems can best be represented not by one person but by two, two scientists who have a common goal but different aptitudes, overlapping but not identical curricula, and two coordinated systems of therapeutic methods. If, in the psycho-biological team of the future, we will train the *psycho* half as well as we have trained its *bio* half in the past; then out of the two could be formed a team which would make of psycho-biology a living reality, a reality not in medicine alone but in our whole culture.

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BOOK REVIEWS

(These reviews represent the individual opinions of the reviewers and not necessarily those of the members of the Editorial Board of this Journal)

The Anatomy of the Nervous System. By STEPHEN W. RANSON AND SAM L. CLARK. 8th Ed. Illus. 532 pp. $6.50. *W. B. Saunders Company, Philadelphia, Pennsylvania,* 1947.

This is the latest revision of Ranson's widely used text, and the first under the editorship of Professor Clark. The book is slightly larger—12 pages and 9 figures have been added—than the 1943 edition, and the general style of presentation is unchanged. Certain chapters and parts of chapters have been reshuffled to increase the integration and continuity of the text. For example, the gross anatomical descriptions, which previously were scattered throughout the book, are here grouped into one chapter. Numerous additions from the experimental literature are found, and the discussion of clinical cases has been partly rewritten and improved. The discussion of cortical localization has received much needed attention, but the significant, recent contributions to sensory localization are still sadly neglected. The reviewer's special interest in the histogenesis of nervous tissue, and in the motor system of the spinal cord is unsatisfied by this part of the book, because of the editor's neglect of many important contributions. The recent histochemical studies of chromatolysis are not mentioned here. Many of the papers cited in the text have not been added to the bibliography.

The new editor should be complimented on the improvement of this volume over its already excellent predecessor, and it is to be hoped that the few still patent weaknesses will be corrected in future editions.

J. M. S.

The Compleat Pediatrician. By W. C. DAVISON. 4th Ed. 256 pp. $3.75. *Duke University Press, Durham, North Carolina,* 1946.

This is the fourth edition of Dr. Davison's book. The preface emphasizes the fact that the volume is "an effort to compile and record briefly those practical pediatric facts, which though essential, usually slip from memory." The Compleat Pediatrician does contain an amazing amount of useful information, clearly stated and readily available. There are sections which list the diseases involving the various systems of the body, briefly enumerating the important signs and symptoms of each. However, the sections on laboratory procedures, general treatment and nursing, drugs and prescriptions appear to be of most practical value and cover material which is usually lacking in standard pediatric text books. Such techniques as cisternal puncture, parenteral administration of fluids, skin testing, etc., are rather fully described and make the book most useful to the interne in pediatrics

or to the practitioner who is required to carry out these procedures. In the section on laboratory methods are listed tests in common use in the study of diseases of children, given in sufficient detail to warrant its use as a laboratory manual. The practicality of this little book may be illustrated by the fact that it even includes a section listing essential drugs and equipment for a pediatrician's bag. The title page of the Compleat Pediatrician states that it is written for the use of medical students, internes, general practitioners and pediatricians. The book appears to be of little value as far as medical students are concerned. It is far too practical for their purposes and by its very nature cannot elaborate on the fundamentals necessary for basic training in pediatrics. As a reference book, the Compleat Pediatrician does have its place in the library of the interne, general practitioner and pediatrician.

S. G.

Chronic Disease and Psychological Invalidism, a Psychosomatic Study. By JURGEN RUESCH. 191 pp. $3.00. *The American Society for Research in Psychosomatic Problems, New York, New York*, 1946.

The authors have investigated the economic, social, physical and psychological factors which influence the course of chronic disease and psychological invalidism. Psychoneurotic patients without physical symptoms were excluded and the symptoms had to persist over a period which exceeded the time commonly needed for recovery.

There were 187 cases ranging in age from 13 to 73 years with a mean age of 35.3 years. In 91% of the cases of delayed recovery there was reported 1: pain in a variety of locations. 2: gastrointestinal symptoms. 3: anxiety features.

Two groups of cases are differentiated. A: those who had a diagnosed or identified disease. B: those who never did. The former group is comprised of individuals who have "physical disease with psychological complications" while the latter group consisted primarily of "psychoneuroses with physicalc omplications."

In 73% of the patients there were self-destructive tendencies found as being significant for their delayed recovery. Only 15% of the patients experienced impersonal or external change in their life situations as compared with 45% of the patients who were exposed to significant alterations in their intimate, human environment.

There is included an account of the pertinent psychological problems in general medicine.

This monograph can be highly recommended to every student of medicine. The surgeon, who is confronted with patients who are overly-anxious to be operated upon, or who already have had multiple operative procedures, the orthopedist, who is faced with a patient who is accident prone and who has had a history of more than the expected number of fractures, the physician, who is puzzled by the patient who has a tendency to be "susceptible" to multiple illnesses, will be better able to understand the motivations and character structure of their patients after reading this book.

J. H. C.

Differential Diagnosis of Jaundice. By LEON SCHIFF. Illus. 313 pp. $10.00. *The Year Book Publishers, Chicago, Illinois,* 1946.

Dr. Schiff has organized a very excellent gastroenterological department at the University of Cincinnati and Cincinnati General Hospital. This monograph has the authority of that department as well as of Dr. Schiff's excellent personal reputation. The subject of jaundice is always a complicated one. There are few physical signs in medicine and surgery that are so protean in their causation and mechanism as is jaundice.

The book considers the classification of jaundice, and then considers separately, parenchymal jaundice, neoplastic jaundice, calculous jaundice, retention jaundice, and a separate section on jaundice of the neonatal period. Finally, there are sections on the clinical and laboratory diagnosis of jaundice. The newer tests, such as thymol turbidity received adequate notice.

The work of Rich and of McNee is given due credit, and the book is furnished with an adequate and extremely up-to-date bibliography. It can be safely recommended as profitable reading to all practitioners and students.

H. H.

Diseases of the Retina. By HERMAN ELWYN. Illus. 587 pp. $10.00. *The Blakiston Company, Philadelphia, Pennsylvania,* 1946.

This volume is divided into eight sections dealing with disturbances in circulation, vascular malformations, hereditary changes, inflammatory diseases, tumors, conditions leading to retinal detachment, developmental anomalies and injuries of the retina from radiant energy.

The volume is well written, the subject matter is comprehensive, there are well constructed descriptions of many disease entities which, heretofore, have either been ignored or inadequately described in the conventional text-books on ophthalmology. The book is, therefore, thoroughly worth while and merits a place in every ophthalmological library.

There are, however, definite weaknesses in some of the presentations. First, there is too often a tendency to consider the retina as a separate structure especially vulnerable to certain morbid processes, rather than as an integral part of a complex organ subject to the general pathologic processes, infection and resistance, which affect the body as a whole. Thus the chapters on syphilis and tuberculosis of the retina appear quite inadequate. A similar criticism may be registered against the chapters on vascular diseases. For example, serious exception might be taken to the definition that "arteriosclerosis or hardening of the arteries is one and the same disease whether the intima presents an ulcer containing mush, an 'artheroma', a localized fibrous thickening, or a hyaline thickening of the arterioles", and to the subsequent discussion based on this premise. Second, on contraversial subjects as a rule only one side of the question is presented, and, while there is a bibliography at the end of each section, this is usually incomplete and gives only the literature utilized in this presentation, or which coincides with the author's opinion.

Despite these criticisms, which in essence are really only a reflection of the

author's individual views, this book brings together in one concise volume a mass of material and wealth of information, much of which has been pretty well buried in the literature. Despite its shortcomings, it is a commendable piece of work and is to be recommended to ophthalmologists.

A. C. W.

Early Ambulation And Related Procedures In Surgical Management. By DANIEL J. LEITHAUSER. 232 pp. $4.50. *Charles C Thomas, Springfield, Illinois,* 1946.

This volume dealing with a currently controversial and live subject is written by an author who has been one of the leading and most uncompromising proponents of his subject, and one to whom much credit must go for the spread of the "gospel" he preaches. Claiming no originality for this theory, he propounds in logical sequence the reasons why "early rising" prevents complications and hastens convalescence. He insists upon his definition as meaning "immediate" (i.e. day-of-operation) rising and decries the attitude of his compromising colleagues who follow an attitude of "wait and see" or "happy medium". Ambulation includes not only standing and walking, but coughing in the upright position with the clearing of mucus and disappearance of rales. Chapter by chapter he tersely and convincingly reviews the ordinary groups of complications, and, supported by an experience of 2047 patients shows the beneficial effect of his program. Finally, he puts forth a plan of surgical management based upon his own experience which he considers essential before early ambulation may be permitted. This includes details of preoperative care, anaesthesia, surgical technic including suture material, postoperative care, and finally, the details of early rising itself. This is a brief treatise, well documented with modern references to support the thesis, a convincing treatise which every doubting surgeon should read so that he may better understand the problem which is being attacked and the position of a practical surgeon who speaks with authority about a radical departure in surgical practice.

S. McL.

Harvey Cushing. By JOHN F. FULTON. Illus. 754 pp. $5.00. *Charles C Thomas, Springfield, Illinois,* 1946.

This is the story of one of the great men in medicine. If it is read, not word by word, but with understanding, the medical student will get an inspiration that will greatly aid him to rise above mediocrity and climb to the top of the ladder in his chosen profession. The secrets of success, as exemplified in the life of Harvey Cushing, are a strong healthy body (he was an exceptionally good athelete in the gymnasium, on the baseball field and at tennis), a charming personality that won for him friends in all parts of the world, and a broad basic education. From his youth he was a perfectionist, and throughout his life he took infinite pains to make his addresses, his publications and his care of patients as near perfect as it was possible to make them. He was a firm believer in the value of clinical research,

supplemented, where additional knowledge could be gained, by animal experiments. His pioneer work on the functions and diseases of the pituitary gland is a striking example of his brilliant mind.

Added to these characteristics was the stimulus he received from years of close association with Halsted, Osler, Welch, Simon Flexner, Mall, Councilman and others during the early years of the Johns Hopkins Medical school and hospital. From these men he acquired the curiosity to find out why, and the ambition to be a contributor, rather than a parasite living and practicing on the fruits of the labors of others.

The ambition thus acquired never left him, but grew year by year. Osler interested him in the history of medicine. This lead to the remarkable collection of books and manuscripts, which he left to Yale University. He not only collected these books, but educated himself to read them in the original. He was an inspiring and fascinating teacher. On ward rounds he invariably showed students books illustrating the growth of knowledge throughout the centuries concerning the malady of the patient under discussion.

He was impatient of carelessness and lack of consideration for the patient. He emphasized, often with stinging rebukes to his house officers, that no effort must be spared to give the sick patient the best that is in you, regardless of race, color, creed or financial status.

I know of no medical biography that can be read with greater benefit to the student than John Fulton's life of Harvey Cushing.

S. J. C.

Introduction to Surgery. By VIRGINIA KREELAND FRANTZ, AND HAROLD DORTIC HARVEY. 216 pp. $2.50. *Oxford University Press, New York, New York,*

This stimulating and provocative monograph is an outgrowth of the introductory course in surgery given to medical students in their second year at the College of Physicians and Surgeons of Columbia University. Most of the text is concerned with the reparative process of the tissues in response to injury and/or infection. The reviewer is heartily in accord with the authors in their desire to create in the student an inquiring and critical mind, unhampered by the acceptance of dogma. Nearly every paragraph in the monograph provides, in the words of the authors, "food for thought and basis for argument". Students and young surgeons will profit from a thoughtful reading of this excellent little book.

E. S. S.

Chemotherapy, Yesterday, Today, and Tomorrow. By SIR ALEXANDER FLEMING. 39 pp. $.50. *The Macmillan Company, New York, New York,* 1947.

In his Linacre Lecture, Alexander Fleming has simply and effectively told the story of chemotherapy as it has unrolled during the past century. This lecture is factual, coherent and interesting. It makes excellent reading for both the physician and the layman.

P. H. L.

Medical Biochemistry. By MARK R. EVERETT. 2nd Ed. 767 pp. $7.00. *Paul B. Hoeber, Incorporated, New York, New York,* 1946.

For the first edition of this work, the author expressed the ambition to make it "a text in consonance with modern teaching, which includes the essential facts and fundamental data, . . . and is of such a size that the student will have time to read it." The plan seems to have been abandoned in this, the second, edition which sets out to accomplish two rather irreconcilable objectives. The book seems now intended to serve both as a convenient reference volume and as a text for various types of medical biochemistry courses, including the basic course.

The ten chapters deal with: acid-base relations; colloids, enzymes, and oxidation; digestion; lipids; carbohydrates; proteins; prosthetic radicals of proteins; inorganic substances; vitamins and avitaminoses; and, hormones and endocrinoses. In most cases, each chapter is subdivided under the headings, chemistry, metabolism, and pathology, and closes with a selection of representative general references. The text and the numerous tables present a great mass of information, the reliability of which, in the absence of specific references, is not always easy to assess. For example, only the more experienced student would be suspicious of the curious information that oxyhemoglobin has a pK of 6.62 and hemoglobin a pK of 8.18.

The exposition of subject matter is generally didactic, and often exceedingly brief. One finds little of the lucid and cogent exposition needed in the elementary training of students in medicine. The treatment of acid-base relations is somewhat archaic. The subject of digestion is properly allocated to a separate chapter, whereas the equally, if not more, important subject of the respiratory functions of the blood is scattered as parts of several different chapters. This scattering is perhaps justifiable from a narrow standpoint of "systematization", but it hardly meets the need of the medical student for an integrated concept of one of the more significant aspects of medical biochemistry.

Many of the numerous tables contain interesting and important data in condensed form, some of which the teacher or investigator may find useful.

B. C.

Muscle Testing. Techniques of Manual Examination. By LUCILLE DANIELS, MARIAN WILLIAMS AND CATHERINE WORTHINGHAM. Illus. 189 pp. $2.50. *W. B. Saunders Company, Philadelphia, Pennsylvania,* 1946.

Manual muscle testing is an important division of Physical Therapy and is studied both qualitatively and quantitively. This volume presents muscle topography, muscle function, joint range, and nerve distribution and utilizes 349 diagrammatic line drawings. The physical therapist will appreciate the clear, succinct instructions and the admirable, simple illustrations.

This useful work will be welcomed by physical therapists, by orthopedists, and by other students of the skeletal structure.

T. P. S.

New Aspects of John and William Hunter. By JANE M. OPPENHEIMER. 188 pp. $6.00. *Henry Schuman, New York, New York,* 1946.

This book, in a limited edition, is well printed, well illustrated, well annotated, and more important, very well written. It is a worthy addition to the already extensive literature about the earlier of the two most famous pairs of medical brothers. In the present volume, the first part considers an investigation of the facts leading up to Sir Everard Home's destruction of the John Hunter Manuscripts. With well supported logic, Dr. Oppenheimer convicts Home of burning these manuscripts to cover his own extensive plagiarisms. Since the burning occurred thirty years after Hunter's death, there was ample time to cull the manuscripts for their best, which may have been the basis of Home's own over one hundred publications.

The second part discusses William Hunter's relationship with his lay contemporaries, a subject previously much neglected.

This reviewer's only criticism of this excellent book is that the annotations are placed, undoubtedly for the sake of appearance, at the end of each section. Since they are all of great interest to careful readers, their correlation with the text involves a deal of page turning. This book should be of interest to all medical historians and particularly to all those who have puzzled about various unsolved mysteries in the lives of the two Hunter brothers.

H. N. H.

Outline of the Spinal Nerves. By JOHN FAVILL. Illus. 191 pp. $3.75. *Charles C Thomas, Springfield, Illinois,* 1946.

This little book will undoubtedly prove to be very useful to neurologists and to neurosurgeons. The author has collected all the information about the anatomy, composition and function of the spinal nerves as well as the skeletal muscles. All of the standard text books have been analysed and compared. Where these authorities differ, the author has made his own choice. These facts are presented very briefly but in such a systematic fashion that it is easy to find the information desired.

F. R. F.

Uterine Contractility in Pregnancy. By DOUGLAS P. MURPHY. Illus. 134 pp. $5.00. *J. B. Lippincott Company, Philadelphia, Pennsylvania,* 1947.

This small volume of 134 pages covers observations with the Lorand tocograph on the uterine activity of 1153 individuals during both pregnancy and labor. Many of the records and observations have been previously published in various scientific journals.

The format is excellent. The book is divided into six sections of several chapters each. These divisions are logical for a study of this type and include a discussion of material and methods and a general summary. In addition there are observations on spontaneous uterine activity and factors influencing this activity,

during pregnancy and labor. There are two major criticisms of this work. The first is a lack of thoroughness of discussion regarding the tocograph itself. No real investigation appears to have been made to determine the degree of variation inherent in the instrument itself, or the effect of its positioning or methods of attachment to the abdomen. Using more sensitive devices all of these factors appear to play an important role and there is no reason to suppose that the tocograph is immune to this variability. Nor is the discussion of what is measured by this instrument convincing. Apparently the author accepts without reservation the work of Wolfe that the degree of uterine hardness is what is recorded.

The second major criticism is based on the conclusions drawn. So long as observations are presented these make contributions to our knowledge and are of great interest. The division of pregnancy into three phases of uterine activity, the study of types of uterine inertia as related to tocograph charts, the effects of morphine, estrogen and pituitrin on these graphs are all valuable and important contributions. There is no proof, however, that the statement that the early appearance of uterine activity is related to the duration of pregnancy is valid. As regards the use of the statistical method to prove that early contractions influence the duration of labor, the samples are so small as to make such an approach not only unjustified but meaningless. For example, the duration of labor in primigravidae with early contractability is based on but three cases. Similarly, the character of the uterine response to pituitrin and its relation to the duration of labor is submitted to statistical attack which is invalid on the same basis.

The importance of this volume is in its emphasis on our lack of knowledge of uterine physiology during normal and abnormal labors. While many of its conclusions are not proven certain observations are of importance. With more sensitive and accurate instruments and a study of a great many more cases, and with this small volume as a guide post those phases of uterine activity about which we today know so little, should become clear.

L. M. H.

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Anesthesia in General Practice. By STUART C. CULLEN. Illus. 260 pp. $3.50. *The Year Book Publishers, Chicago, Illinois,* 1946.

Allergy in Theory and Practice. By ROBERT A. COOKE. Illus. 572 pp. $8.00. *W. B. Saunders, Philadelphia, Pennsylvania,* 1947.

The Anatomy of the Bronchial Tree. By R. C. BROCK. Illus. 96 pp. $12.00. *Oxford University Press, New York, New York,* 1946.

The Anatomy of the Nervous System. By STEPHEN WALTER RANSON. 8th Ed. Illus. 532 pp. $6.50. *W. B. Saunders, Philadelphia, Pennsylvania,* 1947.

An Integrated Practice of Medicine. By HAROLD THOMAS HYMAN. Vols. 1–4 and Index. Illus. 4131 pp. $50.00. *W. B. Saunders Company, Philadelphia, Pennsylvania,* 1946.

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Muscle Testing. Techniques of Manual Examination. By LUCILLE DANIELS, MARIAN WILLIAMS and CATHERINE WORTHINGHAM. Illus. 189 pp. $2.50. *W. B. Saunders Company, Philadelphia, Pennsylvania,* 1946.

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125 cc. flasks
for hospitals

1 LITER (1000 cc.)
AMIGEN 5%
IN 5% DEXTROSE SOLUTION
WARNING: Do not use if the solution is cloudy or if sediment is present. The contents of this bottle must not be used for more than one infusion. For storage, keep the unopened bottle in a cool place.
Test No.
MEAD JOHNSON & CO.
EVANSVILLE, IND., U.S.A.

COUNCIL-ACCEPTED
AMIGEN
for parenteral administration of amino acids

The function of Amigen and Protolysate is to supply the amino acids essential for nutrition. Both can be given in place of protein when protein cannot be eaten or digested, or in addition to protein when the protein intake is insufficient. Administered in adequate amounts, they prevent wastage of protein, restore previous losses, or build up new body protein.

COUNCIL-ACCEPTED
PROTOLYSATE
for oral and tube feeding of amino acids

PROTOLYSATE
For Oral Administration
A dry enzymic digest of casein containing amino acids and polypeptides, useful as a source of readily absorbed food nitrogen when given orally or by tube. Protolysate is designed for administration in cases requiring predigested protein. The mode of administration and the amount to be given should be prescribed by the physician.
MEAD JOHNSON & CO.
EVANSVILLE, IND., U.S.A.

1 lb. cans at drug stores

Like Amigen, Protolysate is an enzymic digest of casein and consists of amino acids and polypeptides. Like Amigen, Protolysate supplies the nitrogen essential for maintenance, repair and growth.

Unlike Amigen, which may be employed both orally and parenterally, Protolysate is designed only for oral use.

MEAD JOHNSON & CO., EVANSVILLE 21, INDIANA

There is no shortage now of AMIGEN for parenteral use. There is no shortage now of PROTOLYSATE for oral use.